INDUSTRIAL TOXICOLOGY

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FOREWORD

A characteristic of American industry, a potent factor that has been responsible for its great success in increasing production, improving the product and decreasing its cost, has been the continued development of new methods involving the utilization of hitherto unused, often hitherto unknown, materials and chemicals. Whenever a new material or chemical comes into use, consideration has to be given to its possible or probable effect on those in contact with it during the processes of its manufacture and in the subsequent use of the product. Is it in any way harmful to those who come into contact with it? Can this harm be prevented or so minimized as not to be a danger? What effects can be expected from any material or chemical newly introduced into industry? How can any injurious effects that may occur be recognized? What can be done to prevent them from causing injury? How should they be treated when they occur? These are questions that must be answered by those responsible for the health of workers and by those responsible for the health of those who will use the manufactured product. The physician of the worker often is the first to see evidences of injury to the worker.

The subject of industrial toxicology, i.e., knowledge of injurious actions of substances used in industry, always has been important. Now with rapid changes being made in the methods of industry, this importance has been enhanced very greatly. Many physicians are confronted with the problems of the diagnosis and treatment of injuries and diseases developing in workers by reason of conditions associated with their work; this applies both to the physician employed by a given industry to care for its employees and to the general practitioner, who may be consulted by a worker. All of this makes very timely the publication of this concise volume on Industrial Toxicology written by Drs. Alice Hamilton and Rutherford T. Johnstone, who have had very extended experience in industrial toxicology as indicated by the data following their names on the title page of this volume. The editor believes that this book will be found very useful to many practitioners of medicine.

Henry A. Christian
Editor of Oxford Medicine

CHAPTER XIX

INDUSTRIAL TOXICOLOGY

By ALICE HAMILTON and RUTHERFORD T. JOHNSTONE

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PART I

PATHOLOGY AND DIAGNOSIS

BY ALICE HAMILTON

INTRODUCTION

There are certain features in which industrial toxicology differs from general toxicology. These may be grouped under three heads, under the first of which would come the mode of entrance. In ordinary poisoning the usual channel is through the mouth; the poison is swallowed accidentally or intentionally. Next in frequency is the inhalation of poisonous gases, and the path through the skin is comparatively unimportant. In industrial poisoning the relative importance of the different paths of entrance is quite different. Inhalation of vapors, fumes and dusts is much the most important; then comes absorption through the skin, while the least important of all is ingestion through the mouth.

Gases and vapors, which enter through the respiratory tract, are very numerous in industry. Some are compounds which have a direct local action on the tissues they reach. The heavy acids may act in this way when, through some accident, a spray of tiny droplets is thrown into the air. This is also the mode of action of the nitrogen oxides and of sulphur dioxide, all of which have a caustic action, which may be confined to the upper air passages or may involve the whole lung tissue. Other gases, without producing a local action, pass from the lungs into the blood. In this group belong the asphyxiating gases, CO, CO_2, HCN, H_2S, the petroleum distillates and a large number of petroleum derivatives, benzene and its homologues.

The most dangerous form of arsenic is not white arsenic but hydrogen arsenide, which is given off in gaseous form, when one of the heavy acids, usually sulphuric, less often hydrochloric, comes in contact with an arsenic-bearing metal, zinc or iron, an accident not at all rare in industry. Mercury volatilizes at room temperature, and mercurial poisoning in industry usually is caused by inhaling volatilized mercury, although absorption may take place also through the skin. In poisoning from white phosphorus fumes are chiefly important, although the poison may be conveyed also to the mouth by phosphorus-smeared fingers.

Metal fumes are finely divided particles of sublimed oxides produced by heated metals. These enter the body through the inspired air, and it is in this

way that industrial poisoning from metals usually occurs. A similar danger is the inhalation of finely ground dust.

Skin absorption is important chiefly in connection with the coal tar derivatives, aniline, the nitrobenzenes, the phenols, the compounds of toluene, of which trinitrotoluene is the most widely known. Others belong to the petroleum series, methyl alcohol, carbon tetrachloride, triorthocresyl phosphate and others, which produce industrial poisoning both through fume inhalation and through skin absorption. Naturally it is difficult to decide just what part is played by the skin in the case of a volatile compound, because, whenever there is skin contact, there is also a possibility of fume inhalation, but with regard to the coal tar derivatives skin absorption seems decidedly the more important.

Industrial poisoning by direct ingestion is of negligible importance. Painters, white lead workers, makers of storage batteries may poison themselves by eating lead-soiled food or getting lead on their chewing tobacco, and it would be possible for men working with white arsenic or Paris green or the arsenates to be poisoned, if they eat with unwashed hands. Probably mercurial poisoning sometimes takes place in this way, but such cases are neither so common nor so severe as those that follow exposure to fumes or dust.

A second difference between industrial poisoning and non-industrial is that the latter usually is acute, the former usually chronic. It is true that the occasional acute case of poisoning in industry attracts more attention, because it is startling, and it is clearly connected with the occupation, while the chronic case is not dramatic, and its connection with the occupation is often far from clear. Nevertheless chronic cases are not only far more numerous than acute; they are also sometimes more serious. Acute benzene poisoning is very rare nowadays, and if it does not kill, it almost never leaves behind a lasting injury, but chronic benzene poisoning occurs with much greater frequency and is far more serious. It is in the slow, chronic forms of mercurialism that we see palsies and psychoses, not in the acute, and the same is true of carbon disulphide poisoning.

This is one reason why experiments on animals do not throw much light on the problem of industrial poisoning. The acute effects may be reproduced fairly easily but not the effects of tiny doses repeated throughout the years.

The third important difference between ordinary toxicology and industrial is that the former usually deals with one poison at a time, while the latter often has to deal with a mixture of toxic bodies, which produce a complex and confusing picture. The temptation is to simplify, to pick out one poison and attribute all the symptoms to it, but error may lie that way. For instance, a case of brass poisoning may be very much complicated by the presence of lead in the alloy. Printers, who use type containing lead and antimony, and rubber compounders, who handle lead oxide and the sulphides of antimony, may, of course, suffer

poisoning from either of these substances, but it seems hardly safe to diagnose a case of pure antimonial poisoning in such a workman and not to regard it as a mixed case. Even more puzzling is the problem with regard to the mixtures of volatile poisons, so much used in industry, the coatings, which contain members of the coal tar series and the fatty series, the paint and varnish removers, the dry-cleaning mixtures and the great variety of compounds, which may be encountered in a single department of anilin dye manufacture.

Finally, in considering industrial poisoning, it is necessary to remember that there are factors in industry which distinctly favor the action of toxic compounds by lowering the resistance of the body, increasing the possibility of absorption or interfering with elimination. Heat and humidity help absorption through the skin and aid in the volatilization of the lighter poisons; heavy work increases the amount inhaled by increasing the depth of respiration. Long hours mean a larger dose of poison, for obviously a man can absorb more dust or fumes in ten hours than he can in eight. Since indigestion with constipation interferes with elimination, poor food becomes a factor of decided importance, and since absorption is much more likely to take place from a fasting stomach, the kind of breakfast taken by the workers in the poisonous trades becomes important. The British pay far more attention to the feeding of their work people than we do, and in the poisonous trades in England it is customary to provide a cup of milk or cocoa, free of cost, the first thing in the morning and to make it possible for the workers to get a hot drink, usually tea with milk and sugar, in the middle of the forenoon and afternoon and an abundant hot meal at noon. In contrast to this a large number of American workmen in the poisonous trades, especially those of foreign descent, begin work in the morning on a breakfast of black coffee and bread and have nothing at noon but a cold, dinner-pail meal.

The fact that individual susceptibility to poison varies very greatly is well known to toxicologists and always is clearly demonstrated in instances of mass intoxication, such as the famous methyl alcohol poisoning in a Berlin lodging-house from drinking adulterated brandy, when some men died after drinking a quantity of liquor which in others caused only a passing attack of headache and dizziness. In industrial poisoning this varying susceptibility is a very troublesome factor and causes confusion in the mind not only of the employer but sometimes of the industrial physician. So long as the majority of a working force escape the effect of a given poison, it is very hard to convince the employer and sometimes the physician that the man, who does suffer from its effects, has anybody but himself to blame. The employer argues that what is dangerous for one man must be dangerous for all, that a falling scaffold, a stream of molten slag, an electric current, produce the same effect no matter who is the victim. Therefore, if a dust or gas is harmful, all the men should suffer from it. He

always can produce some old and seasoned workmen, who have been with him for many years and have never been ill, and he does not see why he should be responsible for the weaklings who do fall ill. The industrial physician usually argues that, if only a small proportion of the men react to a given poison, it means that those men are more uncleanly in their habits or are alcoholics, although a little investigation might prove to him that neither of these assumptions had any basis. It is curious that men are so much more reluctant to accept this fact of varying susceptibility toward industrial poisons than they are to accept the equally startling variation in susceptibility to infectious diseases. Nobody attempts to explain the cases that occur in an influenza epidemic on the ground of the personal habits of the victims.

Aside from this purely individual variation, there are certain factors that influence the incidence of poisoning. How far race is a determining element we do not know. Legge and Goadby speak of a factory in which Italian workmen show considerably less susceptibility to lead poisoning than do their English comrades, but this lasts only so long as they adhere to their national diet and do not become addicted to alcohol. Negroes are considered by many practical men to be more susceptible to lead and less susceptible to poisons which enter through the skin, such as TNT, than white men, but it has never been possible to prove either of these theories, largely because it has not been possible to compare two groups, white and negroes, doing the same work and having the same living conditions. In our TNT manufacture and shell loading during World War I, it seemed at first that the negroes had decidedly less poisoning than the whites, but when both races had the same housing, ate the same food and used the same bathing facilities, the apparent difference between the two disappeared, and the negroes had their full share of TNT sickness[116]. The French experience with their munition poison, dinitrophenol, was much the same as ours with TNT. At first it seemed that the yellow race, the Annamites, were the least susceptible, and the whites were the most so. But when they took into consideration the different standards of personal cleanliness, the greater amount of alcoholism in the white group and also the greater skill in diagnosis of the men in charge of the whites, they were forced to the conclusion that racial susceptibility had very little to do with it (Perkins[258]).

It is unquestionably true that youth and immaturity influence the incidence and the severity of industrial poisoning. This is recognized in all countries and embodied in legislation, wherever there is legislation for the protection of workers in the dangerous trades. Practically all European countries provide for the exclusion of boys and girls from occupations which expose them to poisons. In the United States such legislation has come more tardily, because it has never been the American habit to employ boys and girls in the poisonous trades, and

the danger has existed in only a few industries, such as printing, type-founding, making lithotransfer paper, making lead seals, soldering and using volatile solvents. A committee representing the Federal Children's Bureau has formulated a model law for the protection of youthful workers against occupational poisoning, which it is hoped will be adopted by State legislatures.

There is much vague evidence as to the greater susceptibility of women to industrial poisoning than men but little that is positive. With regard to lead it seems clear that women, if not actually more quickly poisoned than men (the two sexes rarely do exactly the same kind of work), are more subject to the severer forms of plumbism. As to the other poisons benzene is the only one concerning which it can be said with certainty that it is more dangerous for women than for men, this because benzene attacks the bone marrow, which is more labile in women than in men, and the hemorrhagic tendency in benzene poisoning is likely to cause in girls menstrual hemorrhage and in pregnant women abortion.

Women are not more susceptible to the asphyxiating gases than men, but the war-time experience in England and in this country showed that young women suffered more from ether fumes than did mature men[57]. The same impression holds in Germany with regard to the narcotic chlorinated hydrocarbons, especially trichlorethylene. Little is known about the effect on pregnancy of any industrial poison except lead and benzene, but mercury has been found in the fetal blood as a result of poisoning in the mother.

Inorganic Acids

Sulphuric Acid and SO_2

Sulphuric acid is the most important industrially of the inorganic or "heavy" acids, but it is rarely the source of injury to workmen. Its action is on the upper air passages, but bronchitis and bronchopneumonia have not been traced to such fumes.

Sulphur dioxide is formed in the course of many industrial processes, smelting sulphide ores, synthetic production of phenol, production of sulphuric acid by the chamber process#, refrigeration, bleaching paper, burning coke. To the ordinary person SO_2 is almost irrespirable, but men become accustomed to it fairly easily and carry on in an atmosphere, which is choking and painful to a

This is the older and cheaper process, roasting iron sulphide or sulphur or iron filings from gas works. In addition to the SO_2 fumes there is danger from nitrogen oxide gas which provides an extra atom of oxygen. It is this last that must be held responsible for "gassing" in men who clean sludge from the chambers (see also section on Arsenic). Contact acid is made by the use of a catalyst to effect the final oxidation.

visitor. A dangerous amount in the air sets up a violent reflex which forces the man to escape, and if he cannot, bronchitis, bronchopneumonia, edema of the larynx and lungs may follow.

An accident was reported to one of us (A.H.) involving some 13 men, who were shovelling sulphur from the hold of a vessel, when a spark from a travelling belt ignited the sulphur dust in the air and filled the place with SO_2. Those who were near the exit from the vessel's hold suffered no serious harm, but two men far back in the ship lost their way, and by the time they were brought out, they had breathed enough gas to set up severe bronchopneumonia with incapacitation for some two months.

The use of SO_2 as a refrigerant has led to accidental poisoning but in our experience not of a serious nature. For instance two cases seen by one of us (R.T.J.[156]) were in men who were in a small enclosure where a drum of SO_2 exploded. Their clothes froze at once, and one of them had his right eye frozen, but it returned to normal in four weeks. The other presented a picture typical of bronchial asthma, but after 30 hours the lungs were clear, and he went back to work at the end of four days.

Gordon[63] reported recently an interesting form of SO_2 poisoning, following exposure to the gas from a refrigerator. The immediate irritation died down promptly, but five days later an acute tracheobronchitis developed with a thick, gray membrane which was removed, but the symptoms were slow in clearing up. Three months later he returned to work, inhaled SO_2 again, this time from the fumes of coke, and developed a second attack which ended in a partial stenosis of the left main bronchus.

Chronic poisoning from SO_2 does occur, but apparently it is not common. Haggard[111] believes that immunity is not acquired, that the cessation of irritation to nose and throat comes from a chronic catarrh which produces a tenacious mucus as protective covering for the upper air passages but not for the lung tissue. Kehoe[160] studied the effect of long and heavy exposure on 100 men and found a high incidence of slight nasopharyngitis, alteration of the sense of taste and smell, dyspnea on exertion, increased fatigue, abnormal reflexes and abnormal urinary acidity.

Hydrochloric Acid and Chlorine

Hydrochloric acid gives practically no trouble in industry, but its anhydride, chlorine, is notoriously dangerous.

Chlorine is a greenish yellow gas intensely irritating and damaging to all mucous surfaces and to the conjunctiva. We know of its effects chiefly through its use in World War I, but industrial cases are almost never as severe as war cases were, for in war the men could not escape the gas; in industrial work the

victim knows he is breathing a poison and escapes as quickly as possible. In ordinary cases there is a temporary disability with inflamed throat and burning "deep in the chest" and rarely pneumonia or acute congestion with edema. Chlorine is produced by electrolysis of common salt and sold in containers, the accidental leaking of which is the source of most of the cases of gassing.

Phosgene: $COCl_2$ belongs under this heading, since it breaks up and forms hydrochloric acid when it comes in contact with the moisture of mucous surfaces (Hegler[131]). The special danger of phosgene gas is its non-irritating character, for it does not give warning by a strong reflex, as do chlorine and hydrochloric acid. It is used as a dye intermediate and may be produced by the heat decomposition of carbon tetrachloride and other chlor compounds, chiefly when they are used as fire extinguishers[58] but also when for any reason the fumes come in contact with a naked flame. McNally[243] reports such a case with symptoms of *trichlorethylene intoxication,* to which was added acute congestion of the throat and lungs.

Nitric Acid and the Oxides of Nitrogen

The manufacture of nitric acid and its use in various industrial processes are attended with danger, for the escape of the acid to contact with the air results in the evolution of nitrous and nitric oxide fumes which have a decidedly caustic action on the respiratory tract. Haggard[111] has pointed out that all respiratory irritants have the same toxicological action. The difference in symptomatology is related to the location of their action and is dependent upon the relative solubility of the irritating gases. A gas that is very soluble in water is readily taken out of the inspired air by contact with the first moist tissue it reaches. Hence, the upper respiratory tract bears the brunt of action. A gas that has a low solubility in water is slower to liberate its irritant principle, and the main damage occurs deeper in the respiratory tract. Here nitrogen oxide fumes belong, for their action on the nose and throat is less irritating than that of chlorine or SO_2. Therefore, they do not give warning of danger to the same degree.

During World War I the accidental escape of nitrous fumes was fairly common, because engineers were not yet familiar with the difficulties encountered in its production and use. It is almost impossible to avoid leaks, the acid eating through almost every known substance. The production of high explosives by nitration of cotton, paper, glycerine and starch is attended with the sudden formation of nitrous fumes in the presence of water, or if the temperature is too high. Nitric acid is made by the action of sulphuric acid on sodium nitrate, Chili saltpeter or more rarely, on ammonium nitrate, if atmospheric nitrogen is being used. It is used to make the high explosives, smokeless powder and mili-

tary gun cotton, nitroglycerine and nitrostarch (Trojan powder), nitrocellulose for celluloid, photographic films, lacquers, " dopes ", etc. for etching metals, for various processes in the making of coal tar dyes and drugs and for preparing metals for coating. It is produced accidentally in mines, when the blasting powders burn instead of detonating, or in blasting for tunnelling (Irvine[151]). The increasingly important work of autogenous welding has brought a new source of nitrous fumes, for under the intense heat of an oxyacetylene or electric torch the oxygen and nitrogen of the atmospheric air unite to form oxides of nitrogen.

The action on the respiratory tract is caustic, and there is congestion of the throat, which may result in edema of the glottis, congestion of the bronchi, which may be extreme, and, if the finer bronchi are involved extensively, there is increasing dyspnea, the lungs fill with exudate, and death may come on rapidly from edema of the lungs (Wood[348]). Slower cases develop pneumonia, sometimes not till some days after the accident (Hall and Cooper[113]), or there may be an acute inflammation followed by a fibroid process, bronchiolitis obliterans (Fraenkel[82]), or by tuberculosis. In case the exposure is very great, death may come on within a few hours or even minutes, and the only significant finding at autopsy may be the presence of nitric acid in the blood[115]. Several such cases occurred during the early years of World War I, when conditions in industries sometimes were extremely primitive. The blood in nitric acid poisoning is thick, sticky, tarry, with diminished alkalinity (Doremus and McNally[54]) or acid from the presence of nitric acid. The studies made of the victims of the Cleveland Clinic fire showed that this thickening is not inspissation of the blood, for there is no loss of serum, but is due to an increase in erythrocytes under the stimulus of the pulmonary edema and consequent anoxemia (Muntwyler and Associates[231] and La Towsky and Associates[180]).

The following history from a guncotton plant in 1917 is typical of nitrogen oxide poisoning (A.H.). A man was working in the nitration shed, producing military gun cotton, which requires 100 per cent. nitric acid. A centrifuge blew up, and the heavy lid knocked him senseless. The other men fled at once but did not miss him immediately, so that he was exposed to the fumes for some minutes before they dragged him out. Still, when he came to in the fresh air, he did not feel that he had been injured, and after the then usual first-aid treatment, a few drops of chloroform in water with aromatic ammonia to quiet the spasmodic cough, he went home. During the night he woke, feeling he was being strangled, and when the physician saw him, he was propped up in bed, his face livid and terror stricken, his air hunger increasing, unable to speak or move. He had complained earlier of gastric pain, but that was submerged by his air hunger. In spite of a rather tardy administration of oxygen he died of edema of the lungs in less than 24 hours after the accident.

The American Standards Association has set 25 parts per million as the maximum allowable concentration of oxides of nitrogen*.

Hydrogen Fluoride and the Fluorides

This very corrosive acid, hydrogen fluoride, sometimes is used instead of sandblasting for preparing metal for coating by " pickling ", for cleaning sandstone and marble, removing porcelain enamel, frosting glass. It has displaced the sandblast also in frosting electric light bulbs. The effect is that of a powerful caustic.

An unusual case of injury from hydrogen fluoride was the following (R.T.J.): A man, who had fallen and broken a small bottle of the acid, had received splashes on face, hands, left arm and left thigh and, half an hour later, was admitted to the hospital with burns of a second degree in all these areas, but the fingers of the left hand were blanched, at first, then soon grew dusky. The next morning they were gangrenous, and eventually all the distal phalanges had to be amputated.

A new use for hydrogen fluoride has come to light recently, as a catalyst in the production of high octane aviation fuel. This is said to provide a very difficult problem for safety engineers.

Fluorides are used in smelting steel and aluminum and are given off in the production of superphosphate from phosphate rocks. Most of the cases of fluorism have come from the recovery of aluminum from cryolite[195].

The French were the first to describe " fluorisme " or cachexia fluorica as seen in miners of cryolite, a double fluoride of sodium and aluminum with some 54 per cent. fluorine (Feil[72]). The chief characteristic of this form of industrial poisoning they found to be sclerosis of the bones, resulting from the fixation of calcium by fluorine. Soon after this Moller and Gudjonsson[295] made the same discovery in Swedish miners and Roholm[265] published an exhaustive study of the bone changes, thickening of the bone laminae, opacity of the bones by x-ray and calcification of the ligamental attachments. The appearance in roentgenograms is said to have been noted first by Moller in 1931 in the course of an examination of cryolite miners for silicosis.

* A committee, Z37, of the American Standards Association for some years has dealt with the task of determining the " maximum allowable concentration " of the most important industrial poisons. When mention of such a standard is made here, it must not be forgotten that these are calculated on the amount of air inhaled by a worker, when breathing at an ordinary rate, for eight hours. Heat and heavy work increase both the rate and the depth of respiration and so hasten the absorption of the poison. Zangger of Zurich, an authority on volatile poisons, says there is always more trouble from their use in hot weather and in southern climates. American experience confirms this abundantly. Of course heat also favors the evaporation of a solvent.

Roholm[265] describes chronic fluorisme as having clearly defined diagnostic signs, mottled enamel of the teeth, osteosclerosis and osteomalacia. In addition one should look for general symptoms, anorexia with loss of weight, anemia, perhaps from encroachment on the bone marrow, and cachexia. He found diffuse osteosclerosis in 84 per cent. of the workers in cryolite, but Brailsford[21] examined 49 Scotch cryolite miners exposed for many years and found no sign of it.

According to Brun and his colleagues[25] cryolite workers excrete fluorides in large quantities in the urine for some years after exposure has ceased, probably from breaking down of pathological bone tissue, for such men show less osteosclerosis than do working miners. They believe that daily intake of as much as 28 mgm. over many years is needed to produce osteosclerosis.

One of the few American studies of " fluorosis " in man is that of Bishop[14], who was examining a group of 78 cryolite miners for possible silicosis. Thirty-nine of them showed evidence of first or second degree silicosis, and over half of these presented definite bone changes in roentgenograms, varying from a " fleecy thickening of the bone lamina and an increase in the whiteness of the bone shadows to an actual opacity of the bones and calcification of the ligamentous attachments ".

Chromic Acid and the Chromates

Chromic acid and the *chromates* present problems to the engineer more than to the physician. Chrome ulcers, known as chrome holes, form on the skin and may penetrate deeply, but they are not very painful, and they never suppurate, the acid apparently acting as an antiseptic. Nor has there ever been a case of epitheliomatous degeneration reported, although thousands of chrome ulcers have been observed in England and in Germany. The lesions caused by chromium compounds are characteristic and visible, which is probably the reason why this form of occupational poisoning has attracted much more attention and is surrounded by a much greater degree of protection than its importance deserves. Aside from the skin ulcers there is involvement of the nasal mucosa with chronic inflammation, a purulent discharge, the formation of crusts and some difficulty in breathing but rarely much more than that. Ulcers then form, painless and slow, confined to the cartilagenous portion of the septum and ending in perforation but never in deformity (Blair[15], Bloomfield and Blum[16], Dixon[52]). The American Standards Association has suggested 1 mgm. per 10 cu. meter as the maximum allowable concentration for chromic acid and the chromates.

Alkalies

The alkalies used in industry are numerous, and some of them are very powerful caustics, while all have more or less caustic action on the skin. They present,

however, no problem to the industrial physician, for their control is a matter of engineering skill and good plant practice, and the lesions produced are evident to all. The National Safety Council has prepared several pamphlets on the safe handling of caustic alkalies and the best method of treatment of alkali burns.

The fact that *ammonia* is a gas makes it more dangerous in industry than are the solid caustic hydrates. Accidents from the bursting of an ammonia supply pipe in a refrigerating plant occur from time to time, the severity of the effect depending on the time that elapses before the victims can escape. Legge says that there were reported in Great Britain between 1920 and 1931 74 cases of acute poisoning from ammonia fumes, all accidental, and most of them caused by leaks or breaks in refrigerating plants and in plants recovering nitrogen from the air[183]. According to Henderson and Haggard[136] irritation from ammonia fumes begins at 0.5 mgm. per liter of air, coughing at 1.2 mgm., but for prolonged exposure the limit should be 0.07 mgm. It is, however, a matter of common knowledge that men become accustomed to the fumes to a considerable degree (Flury and Zernik[80]). Both Lehmann and Seifert (see ref. 66) found it impossible to produce chronic poisoning in animals, but Ronzani[267] claims to have set up not only conjunctivitis but keratitis and also a loss of hemoglobin and a lowered resistance to infection, while Horvath[141] goes even further and believes that pleurisy and bronchopneumonia follow the repeated exposure of animals to low concentrations of ammonia.

Aside from refrigerating plants and the manufacture of refrigerators, ammonia fumes may be encountered in storage battery manufacture and in rubber vulcanization, but the fumes are not excessive. Thies[314] says that as long as ten days after an accidental injury to the eye from splashing of ammonia water a severe conjunctival and corneal ulcer may develop, and he describes such a case.

Barium

Men handling large quantities of barium compounds, the sulphide, oxide, carbonate, sometimes complain of irritation of the throat and nose and eyes, for the dust is somewhat caustic. Bertarelli[13], however, who has written one of the few articles on the possible action of barium compounds in industry, says he has never seen any sign of toxic symptoms in workers exposed for long periods to barium chloride. It seems that in Italy this compound is used in treating wool for stuffing mattresses, and carding this wool is dusty work, yet no harm seems to result from it. On the other hand Kipper[163] has described a fatal case of poisoning from barium oxide and succeeded in producing in animals paralyses and an effect on the heart like that of digitalis. Occupational dermatitis from barium compounds unquestionably does occur.

Lead

Lead is looked upon universally as the industrial poison par excellence because of its widespread use, its characteristic effects and the great mass of data concerning it collected from all industrial countries throughout more than a century of study. The lead compounds encountered in industry are, in the order of their importance, the suboxides, litharge and red lead, the basic carbonate or white lead, the basic sulphate or sublimed white lead, the chromate, the sulphate and carbonate, the sulphide, lead tetraethyl and less commonly, the acetate, nitrate and chloride. A large number of industries use metallic lead in molten or solid form, and as this oxidizes rapidly, the workmen are exposed to the lower oxides of lead, which form a coating of finely divided gray powder on the surface of solid metal and an easily detached coating of so-called dross on the surface of molten lead.

These compounds differ decidedly in their toxicity, an important point in the prevention of lead poisoning in industry. It is not nearly so necessary to guard against dust in the lead mines of Missouri, where the ore is lead sulphide, very slightly soluble in human gastric juice (see Carlson and Woelfel[33a]), as it is in the mines of Utah, which carry the much more soluble carbonate and sulphate. Lead glaze for pottery gave rise to much plumbism so long as raw white lead, the basic carbonate, was used, but when the white lead was changed by fritting, i.e. fusing and granulating, to the insoluble disilicate, that danger disappeared.

The toxicity of a given lead compound depends on (a) the solubility in the body fluids and (b) the fineness of the particles, for the finer they are, the more quickly do they dissolve. A lead compound such as the acetate, for instance, which when swallowed is very toxic, may be industrially harmless because it is sticky, not dusty.

Various estimations of the relative toxicity of these compounds have been made. Fairhall[71a] recently published the results of exhaustive tests on animals to determine the relative toxicity of the most important lead compounds. From inhalation experiments on guinea pigs he concludes that, while no exact numerical order can be assigned to the various compounds, certain of them may be set apart as more toxic than others. Thus the carbonate, monoxide and sulphate seem more toxic than metallic lead or other compounds. Lead arsenate is very toxic, but this is due to the arsenic radicle. The chromate is less toxic.

Some twenty years ago an effort was made in this country and in England to press the use of "sublimed white lead", which is the basic sulphate, in the place of "old Dutch process white lead", the basic carbonate, on the ground that the former was non-poisonous. Carlson and Woelfel[33a] tested the solubility of the two in human gastric juice and found that the basic sulphate is soluble, averaging 24.7 to 30.0 per cent., while the basic carbonate averages 59.8 to 77.9 per cent.

Later the same question arose in Germany and led to several investigations of the claim that the sulphate is a safe pigment. Lehmann[185a] and Koelsch and associates[169b] fed animals with the two compounds, and both found little, if any, difference in their toxicity.

Lead borosilicate, present in fritted ceramic colors, is insoluble in water, but Beebe and Mallette[12c] have shown that it can be found in the liver and skeleton of animals exposed to a spray mist of colors such as are used in industry. The new explosive, lead azide, was tested by Fairhall and associates[71c], who found that absorption and distribution are the same as for other lead compounds, but the acute toxic action is caused by the azide radicle rather than the lead. It is decidedly less toxic than sodium azide. Lead acetate, nitrate and chloride are all highly soluble, even in water, but fortunately they do not form dust readily, nor are they industrially important.

Lead tetraethyl differs from all the other forms of lead, which are used industrially, in that it is volatile and highly soluble in lipoids and, therefore, acts markedly on the central nervous system. It is also the only lead compound which is known to be absorbed through the skin.

The industries in which lead is produced or used are too numerous to list, and the majority are too well known to make this necessary. It may be well to emphasize a few points in connection with its industrial use which are not so generally known. For instance the danger of contamination of the air from molten lead does not start at the temperature at which lead vaporizes, but at a much lower point, for whenever molten lead is agitated, as in skimming off dross, dropping in pigs of lead, ladling and pouring, the delicate coating of grey suboxide is detached and floats up with the waves of heat. This is the greatest source of plumbism in printers, for such fumes may come from the remelting kettles, the monotype and stereotype machines, though apparently not from linotypes. In a study of Virginia printing plants recently Homewood and Worsham[140b] found the lead in the air to be within allowable limits except in drossing and sieving when as much as 955 mgm. per 10 cubic meters was found.

It is the suboxide, too, that is produced by the use of the oxyacetylene torch on lead or lead-painted surfaces as in the scrapping of battleships before the war and in welding lead painted ships at the present time (Brown[22d], Tabershaw[306b], Kehrlein[160e]). It is also the suboxide, which constitutes the danger in using solder, either by hand or machine (Lea and Fluck[180c]) and in founding brass or "railroad bronze", which may contain over 25 per cent. lead and is poured at about 1100° C. (Pedley and Ward[249]). Although soldering usually is regarded as a fairly harmless job, I have the history of a man in the Mayo Clinic, who after three years of such work developed a typical attack of lead colic, and shortly thereafter both wrist and ankle drop and "definite evidence of lead encephalopathy". The danger of lead fumes and lead dust in brass foundries has been mentioned under "Metal

Fume Fever". The suboxide forms over the surface of solid lead, though much more slowly than it does on molten lead. This must be guarded against in printing plants and in all places where metallic lead is handled.

The chief uses for white lead, the basic carbonate, often called old Dutch process white lead, are for paint and for pottery glazes and ceramic colors. Much less white lead is used in house painting nowadays. Even in outside paint the white lead is tempered with harmless titanium oxide, and interior work usually is done with lead-free paint. In earlier years lead paint was used for all vehicles, from carriages to Pullman cars; now that is all gone.

The painters' work, which used to be a notorious source of plumbism, witness the phrases "painter's colic", "painter's palsy", is now fairly free from this danger, sometimes wholly free. A lessening of the danger of plumbism for potters also has come in the general adoption, learned from the English, of fritted lead glaze containing almost insoluble lead silicates. The extremely fine particles of ceramic colors contain borosilicates which are somewhat more soluble.

Litho transfer preparation consists in spreading very finely ground lead colors on specially prepared paper. It is recognized everywhere as very dangerous work and commonly employs young women.

The oxides, litharge, red lead and the brown peroxide, are not so soluble as the basic carbonate, but they are very dusty, and it is hard to control air contamination wherever they are used. It is these three oxides that render the making of storage batteries the most prolific source of plumbism at the present time. Litharge finds extensive use in glazes and enamels but no longer in rubber compounding. Red lead paint has come back during the war, especially in shipbuilding. Red lead still is used in the enamelling of sanitary ware but far less than formerly.

Tetraethyl lead is added to motor fuel gasoline in the proportion of one part to 1,300 parts of gasoline, and an organic halogen, usually ethylene dibromide (Humperdinck[142a]), is added also in order to help in the removal of lead from the engine. When it was first produced and blended with motor fuel, there was general ignorance of its dangerous nature and of the ease with which it is absorbed by the human body. It was handled recklessly by experimental chemists as well as by ignorant workmen, and as a result there were cases of acute poisoning of a peculiarly severe type. Eldridge[65a] of the Chemical Warfare Service published in October 1924 the records given him by Thompson and Schoenleben[316a] of severe and fatal poisoning. Kehoe[160b] added records of milder forms, making some 139 cases in all with 13 deaths.

The result of these dramatic occurrences was a widespread fear of danger to garage workers and even to car users, if the gasoline contained tetraethyl lead. Zangger of Zurich demanded that its use be forbidden in Switzerland, and the same demand was made in Britain and in some states of the United States. Since

an impartial inquiry was called for, Surgeon General H. S. Cumming appointed a committee of experts to supervise such an inquiry and assigned members of the Public Health Service to carry it out. The findings were that garage workers exposed to tetraethyl lead showed evidence of lead absorption and storage but not of intoxication; chauffeurs who had used it for two years did not show even absorption (Leake[180d]). The danger to producers and blenders had been controlled already.

Since then, Kehoe and his colleagues[160b] have followed all reported cases of tetraethyl lead poisoning and have kept under observation some 300 men, who have incurred unusually severe exposure to leaded gasoline for some years. These men were examined for physical fitness and signs of lead absorption or intoxication, but no such evidence was found. Kehoe's findings were confirmed by the animal experiments of Kraut and Lehmann[173b].

A secondary danger in connection with the use of leaded gasoline, namely the carbonized products found in the engine, is described by Waniek[322b]. These products may give rise to the more common forms of plumbism, masking the cerebral symptoms of tetraethyl. Kehoe lays stress upon this fact and upon the danger incurred when workmen must clean sludge from storage tanks[160b].

The latest publication on this subject is that of Mortensen[229a], who studied the absorption of tetraethyl lead with radio-active lead as indicator. He found that 16 to 23 per cent. of the lead, which reaches the alveoli, passes into the blood. The lethal dose was found to be from 8.9 mgm. per kgm. with survival of four days to 30.1 with survival of four hours, which is smaller than Buck and Kumso's[25a] figures, 16 mgm. injected into the peritoneum and Kehoe's, 22 mgm. injected into the veins. He found, as did Kehoe and Thamann[160a], that lead tetraethyl is destroyed quickly in the body. Volatile lead disappears from brain, viscera and blood in a few hours.

In considering industrial lead poisoning, it is very important to keep in mind the kind of exposure which is present in different lead jobs. Some involve exposure to very small quantities, which if continued over many years, may lead to chronic intoxication but would very rarely give rise to an acute and severe case of poisoning. Examples of these are most of the processes which use metallic lead, the printing trade, making lead pipe, wire, grids, etc., the plumbers' trade. On the other hand severe, acute cases may occur wherever dust and fumes are excessive as in smelting and refining, the production of white lead, roasting oxides, sandpapering, chipping or burning lead paint, making storage batteries, etc. Colic, palsy, encephalopathy may develop rapidly in such a plant, if precautions are neglected.

The entrance, absorption, storing and excretion of lead were described by Aub and his colleagues[4b, 5, 6a] on the basis of three years of experimental and clinical studies carried on at Harvard between 1923 and 1926. These investigators found

that if lead were given by stomach tube to cats it would be found chiefly in the feces because ingested lead is only partially absorbed, and the greater portion of the fraction that is absorbed is caught by the liver, part of it being then reëxcreted into the intestinal tract with the bile. Therefore, much of the lead that enters the gastrointestinal tract does not really enter the organism at all, but either is eliminated directly or never passes beyond the liver. When lead is administered in this way, very large doses are needed, and the administration must be continued for weeks in order to produce symptoms of intoxication. On the other hand, if lead is given by way of the respiratory tract, severe symptoms appear quickly. There is no such defensive system in the respiratory tract, and absorption takes place easily not only from the alveoli of the lungs but from the mucous surfaces of the air passages, beginning with the nostrils (Blumgart[17a]). Therefore, the great danger in lead occupations is the presence in the air of lead dust and fumes, the latter being really very finely divided particles of dust. Modern experience has amply confirmed the dictum of Tanquerel des Planches a century ago that severe plumbism never follows the handling of solid lead but only exposure to dust and "emanations".

This is a very important fact, especially in connection with the prevention of lead poisoning, for unless dust and fumes are controlled, no degree of personal cleanliness will avail to protect the worker against poisoning. Some 20 years ago, before industrial hygiene had made much progress in the United States, it was possible for one of us (A.H.) to collect histories of 132 cases of that very severe and now rare form of plumbism, lead encephalopathy. All the victims of the acute form had had excessive exposure to dust or fumes.

The *signs* and *symptoms*[4b, 5] of *acute lead poisoning* usually are referable to either the gastrointestinal tract or the nervous system, although we sometimes see cases involving both. There are usually more marked prodromal symptoms than in the chronic cases. These consist in a disagreeable sweetish taste in the mouth, anorexia, nausea, sometimes vomiting, headache which may be severe, disturbed sleep, lassitude and a sense of weakness which is general not localized. Constipation is very common and may be interrupted by diarrhea due to the gastroenteritis so often present in acute cases. After a few days of general malaise and constipation and colicky pains the patient may develop sudden, severe colic. In typical cases colic is accompanied by a rigid abdomen, marked pallor of the skin, an increase in blood pressure and a slow, hard pulse. The constipation usually is obstinate during colic, and there is nausea and vomiting. Such an attack may pass over in a few hours or last several days.

"Encephalopathia saturnina" is used by Westphal[327a] as the term to cover all affections of the brain due to lead such as apoplexy, hemiplegia or aphasia from saturnine arteriosclerosis, coma, delirium, epileptiform convulsions, lead hysteria, lead mania, lead neurasthenia. Oliver[244a] restricts the term to epilepti-

form convulsions caused by lead, in which he is generally followed, although von Jaksch[153a] would reject the term altogether and substitute more precise terminology such as encephalitis, epilepsy, mania saturnina, etc. French authors have reported many cases of lead meningitis, which probably in other countries have been included under the general term of encephalopathy[191a, 229c].

This is fortunately a rare form of plumbism nowadays, although occasionally a case is reported in this country or abroad. It may take the form of intense headache, then delirium, convulsions, coma, followed sometimes by permanent mental impairment or by blindness partial or total, or it may be a slowly progressing, mental deterioration resembling that of general arteriosclerosis and accompanied by a contracted kidney (Westphal[327a], Osler[245b]). A lasting epilepsy followed an acute cerebral plumbism in a case described by Putnam[262a], and a similar one was seen by one of us (A.H.). Injury to one or more of the cranial nerves has been attributed to lead by many authorities. In the United States lead blindness seems to be a great rarity, but in English potteries in the days before strict regulations were enforced Prendergast[261a] found among the cases of plumbism in women potters 7.7 per cent. with total and 10.2 per cent. with partial loss of vision.

Pain in the joints, lead arthralgia, is fairly common and in rare cases may be the most prominent symptom. In Tanquerel's 1,217 cases there were 201 which belonged in this class.

Lead palsy is usually a late occurrence, developing slowly, and it is not accompanied by neuritic pains as is the palsy of arsenic or alcohol. It tends to recovery, if exposure is stopped in time. The localization according to the generally accepted theory of Edinger is determined by the use of muscles; those most fatigued are the most affected. Modern industrial work calls chiefly on the extensor muscles of wrist and fingers, which are not as strong as the flexors and are working against gravity. Therefore, the typical form of lead palsy is wrist and finger drop, but in children and in heavy workers it is ankle drop.

Lead gout is described by German authors, but neither American nor British authors lay stress on it.

That lead is a race poison causing sterility, miscarriage, stillbirth in women has been known for centuries, and the carefully gathered statistics of Oliver[244a] and of several French physicians (see reference no. 117 p. 171) give abundant proof of the harmful action of lead on the germ cell, on the chorionic epithelium or on the fetus through the mother's blood. It is not so well known that lead may produce sterility in the male also by injury to the germ cell, but this fact, which was first brought out by Constantin Paul[247a] in 1860 and more recently by Koinuma[170a] in 1926, is established now beyond doubt. It has been used as an argument against laws providing special protection for women in lead work, but that ignores the

nine months of intrauterine life during which the fetus may receive lead from the mother's blood.

The diagnosis of lead poisoning after decades of study still is a subject of controversy, for though a typical case in a lead worker offers no difficulty, there is an endless variety of forms which this mode of poisoning can take. To sum up the problem briefly, the physician must prove first exposure to lead, second absorption, third intoxication. The first depends on a careful occupational history, the second on evidence that lead has entered the body, the third on evidence that the lead has produced injury to the body.

It is important in these days of legal responsibility for cases of occupational poisoning not to confuse evidence of absorption with proof of intoxication, for the latter must include clinical signs and symptoms of actual illness. Absorption of lead is shown by its presence in the blood and in the excreta and by its effect on the blood cells. To take the last first, the change in the red blood corpuscles, which consists in the appearance of fine blue-black granules after appropriate staining, was described first at the end of the last century by Grawitz[96a], and the use of this aid in the diagnosis of plumbism spread rapidly. Under the name of basophilic stippling it has been the subject of numberless studies, the results of which may be briefly summarized. Basophilic stippled cells are youthful red corpuscles, reticulocytes, (Aub and Associates[5]) which have been altered by the presence of lead in the blood. Lead stimulates the bone marrow to increased production of red blood cells and also increases their destruction (Seiffert and Arnold[284a]). The stippled cells are not peculiar to lead intoxication but occur under many other conditions such as exposure to aniline, carbon monoxide, benzol, even various inert dusts (Lehmann[183a]) as well as in other diseases where there is blood cell destruction and regeneration. These cells may be found also in normal persons not exposed to lead. Sanders[270a] found in a study of 2,231 men employed in oil refining with no lead exposure as many as 32.5 per cent. with stippled cells.

On the other hand a case of undoubted plumbism may fail to show this sign. Teleky[311a] says it fails just when most needed, in the slow chronic form of poisoning; it is definitely present chiefly in the rapidly developing acute cases. Kehoe did not find it in acute poisoning from tetraethyl lead. Yet this change in the red blood cells is of decided value in making a diagnosis of lead absorption, if used with proper reservations; some would say, of intoxication, since there is evidently an effect on bone marrow and circulating blood. In the first place their number in leaded blood is way out of proportion to the degree of anemia. In the second place their presence in large numbers is undeniably significant, although there is wide disagreement as to how large the number must be. It runs from about 500 per million reds (Badham and Taylor[9b]) to over 9,000 per million (Sanders[270a]).

Since stippled cells are damaged young red cells, Jones reasons that a count of reticulocytes will yield earlier results. Mayers[204a] makes the same claim for polychromatophilia, while McCord and his colleagues[209a] look for a clumping of the reticulum in immature cells, basophilic aggregation, an earlier and more dependable sign than stippling.

The changes in the white blood cells are insignificant. A relative lymphocytosis has been described, but it is seen in too many other conditions to be an aid in diagnosis. The degree of anemia is seldom high, even in severe cases, though the author has seen counts as low as 3,100,000 red blood cells.

Absorption of lead is best proved by demonstrating the presence of lead in blood serum and urine in quantities greater than occur in persons not exposed to lead. Detection of lead in the feces is less important, for though it proves lead exposure, it does not prove absorption. Even in blood and urine the lead to be significant must reach a variously determined figure. Fretwurst and Hertz[83b] first announced in 1930 that finding lead in the excreta was not conclusive of plumbism, since they had found in persons not exposed to lead as much as 0.01 to 0.07 mgm. per liter in the urine and up to 0.14 mgm. per liter in the feces. These findings since then have been confirmed repeatedly, and there is now a fair consensus as to the quantity which can be regarded as significant. The New York Industrial Hygiene Division in the State Department of Labor accepts this standard: lead in the urine above 0.1 mgm. per liter, in whole blood above 0.1 mgm. per liter, in feces above 0.08 mgm. per gram of ash.

Webster[325a] of the Public Health Service found in adults with no known exposure to lead an average of 0.03 mgm. per 100 c.c. in the urine. Kehoe and Thamann[160a], who have made extensive studies in this field, accept as the mean lead content for normal persons with no industrial exposure, 0.03 mgm. per 100 c.c. of blood, 0.02 mgm. per liter of urine. In actual lead poisoning one should expect an average rate above 0.21 mgm. per liter of urine[39b].

The presence of hematoporphyrin in the urine has been taken as proof of lead absorption (von Embden and Kleerekoper), but others find it less trustworthy a proof than stippled cells (Aub[5]). Schmidt-Kehl[275c] in a self-experiment found that ingestion of white lead caused an increase in urobilin in the stools which ran parallel to the fall in the red cell count.

The lead line is an excellent sign of lead absorption, but unfortunately it is not often found except in workers with heavy exposure and never in the healthy or the toothless mouth. It must be remembered also that bismuth poisoning produces a similar appearance and so does mercury. Thus Wright[349] found a blue line on the gums of 3 out of 100 hatters exposed to mercury; Glibert[90a] of Belgium found it in 57 or 12.8 per cent. of 463 hatters-furriers.

The line is a bluish black stippling, which appears along the margin of the gums, usually showing most clearly along the lower incisors but often also on

the lining of the cheeks. It cannot be rubbed off but lies within the tissues. It consists of the black sulphide of lead produced by contact of the absorbed lead with the hydrogen sulphide which is formed by the decay of protein matter between the teeth. For this reason it is not found in men who take scrupulous care of their teeth, and Aub observes that rabbits living on vegetables, even when severely poisoned, never have this lead line, while cats eating meat almost invariably show it quite clearly.

For the *diagnosis* of lead intoxication the former tests furnish the ground work. In addition there must be a picture of clinical intoxication based on subjective and objective symptoms. Among the first are increasing fatigue, loss of appetite, especially in the morning, a disagreeable taste in the mouth, indigestion with eructation of gas, increasingly obstinate constipation, headache, disturbed sleep, pains in the joints. Among the signs, which may be looked for, pallor is the most common, a greyish or livid color, familiar to lead workers and out of proportion to the degree of anemia. Tremor seen first in the middle and ring fingers, when they are held in extension, is considered an important sign, and even more important is the detection of extensive weakness in the hand which is used most in work. There may be atrophy of the palsied muscles, but sometimes it is hidden by edema in the tendon sheath. Josephson[157b] found marked tenderness along the ulnar nerves especially in the right arm. Lewey and Weiss[188b] urge the use of a very sensitive test, chronaxia, for the larval stage of lead poisoning. This consists in determining the minimal length of time the galvanic current of standard strength requires to flow so as to induce a muscular contraction. A reaction below normal, a hypoexcitability, according to them is proof of plumbism.

In a study of 381 lead workers made by the New York State Department of Labor Mayers[204a] found 232 with evidence of lead absorption, and of these 222 were active cases of plumbism. Gastrointestinal symptoms were found in 192 with laboratory evidence of lead absorption in 136, disturbances referable to the nervous system in 143 and referable to the muscles and joints in 42 cases.

The picture of tetraethyl poisoning differs from that caused by non-volatile lead compounds. It is more rapidly absorbed than any other compound of lead in industrial use. In severe cases, such as those which occurred in 1923, there is a profound effect on the central nervous system, the symptoms of which are insomnia, delusions, excitement, muscular twitching and jerking, hallucinations like those of delirium tremens, maniacal attacks. Very characteristic in severe cases is a marked fall in blood pressure and body temperature and a low pulse rate. In two cases the temperature rose just before death to 110° F.[65a]. Autopsies on four fatal cases were made by Norris and Gettler[238a], who isolated a volatile lead compound from the brains of two men in whom death had occurred within 24 hours after the appearance of severe symptoms.

Milder forms were reported by Kehoe and associates[160b] and by Machle[194a].

The latter followed for some years 78 cases, which showed such symptoms as early fatigue, sense of weakness, insomnia, disturbing dreams, headache, mental excitement, dizziness, tremors as well as gastrointestinal symptoms.

There is still controversy over some of the lesions attributed to the action of lead, such as various types of kidney disease, general arteriosclerosis with contracted kidney or with gangrene of the extremities, hypertension, peptic ulcer, multiple sclerosis.

Animal experiments with compounds of lead usually show that the kidneys are the only organs to suffer much damage (Fairhall and Miller[71b], Calvery[301b]). Volhard and Suter[320a] say lead is a vascular poison, and its effect on the kidneys is due to a disturbance of renal circulation, a throttling of renal vessels causing anoxemia and degeneration of the epithelium with a gradual thickening of the vessel wall and narrowing of the lumen. Ophüls[245a] produced in guinea pigs severe degenerative changes in the kidneys accompanied by regenerative activity and fibrous thickening of the capsules, enough in some to give a somewhat granular appearance. Vigdortschik[319c] of Leningrad, on the basis of a study of 2,769 men, 1,437 in lead work and 1,332 in non-lead work, found a sclerotic kidney three times as often in the first group as in the second. Baader[9] recently reported that he had seen 3 cases of contracted kidney, which were indubitably connected with plumbism. The kidney is anatomically the same as that of the later stages of glomerular nephritis, is slow in developing, 20–30 years, and is caused by repeated spasmodic contraction of the kidney vessels causing arteriosclerosis. Staehelin[300b] also finds symptoms of contracted kidney in the later stages of the majority of cases of chronic plumbism, while in acute cases albuminuria and casts accompany the colic. Vallery-Radot[319a] saw a case of severe acute plumbism with oliguria, albumin and casts and high blood pressure which developed later into one of chronic nephritis.

Perhaps the most striking evidence of a chronic glomerular nephritis following long after an acute attack of plumbism is to be found in the reports from Queensland, Australia. Early in the century Gibson[88a] had reported many cases of plumbicuocular neuritis among the children in this Australian state, 428 in a period in which only 1 and 4 occurred in other states. Gibson traced the poisoning to the white lead paint on the verandas where the children play, paint which under the very hot sun cracks and powders. The same conditions do not exist in the other Australian states. Some years later it was found that deaths from chronic nephritis in people between 10 and 40 years of age of both sexes were strikingly more frequent in Queensland hospitals than in those of other states, 1,070 per 800,000 population against 449, 368 and 344 in three other states (Nye[238b]).

Not only glomerular nephritis but general arteriosclerosis and hypertonia, which may or may not be accompanied by the former two, have been attributed

to the action of lead especially by the older authorities (reference no. 119 p. 32). Here there is decided difference of opinion. Animal experiments seem to deny that such an effect is produced by lead (Fouts and Page[80c]), but it is never possible to reproduce in animals the slow, long-drawn out exposure to minimal doses which occurs in industrial life.

Two large-scale studies have been made on groups of workmen with regard to high blood pressure. Thus Mayers[204a] in an examination of 381 lead workers found hypertension in 98, 66 of them without an associated arteriosclerosis. She believes that the action of lead on the neurovascular system, causing constriction of the vessels, may be responsible for this hypertension. However, as concerns the incidence of general arteriosclerosis there was no significant difference between the two groups of workmen; the rate was high for non-lead as well as for lead workers.

Vigdortschik[319c] studied 2,769 hospital records of workers, 1,437 in lead, 1,332 in other work. He found systolic hypertonia in 15.7 per cent. of the former and 7.4 per cent. of the latter. Excluding cases of essential hypertonia the difference between the two groups rises to 34.6 per cent. in the 30–39 year group. There were 225 cases of hypertonia associated with kidney changes in the lead group, 99 in the control group. Marked nephrosclerosis was found in 4.1 per cent. of the lead workers, other kidney changes in 8.4 per cent.; the figures for the controls were 1.4 and 3.9 per cent.

A fatal apoplexy in a man with arteriosclerosis and chronic plumbism was described by Ruhl[268b]. There were several cerebral hemorrhages and the blood pressure increased markedly, with increase of cerebral symptoms. At autopsy there were marked arteriosclerosis and contracted kidneys. The man had been a painter for 37 years. On the other hand Aub[5] is sceptical as to the connection between plumbism and hypertension or arteriosclerosis, and Belknap[12c] believes there is no connection.

Baader[9] quotes French and German authors on the subject of spontaneous gangrene in lead poisoning and reports a case that he saw with gangrene of the big toe in a painter. The prognosis is good in such cases.

Another controversial subject is the relation of lead poisoning, especially the gastrointestinal form, to peptic ulcer. Schiff[275b] of Vienna discussed the question on the basis of some 48 cases of gastrointestinal plumbism. He finds the cause to be a condition of intense spastic irritation of the whole visceral nervous system, a condition which is not limited to the period of typical colic but is long-continued as evidenced by the obstinate constipation and by the whole gamut of sensory, motor and secretory disturbances, gastralgia, vomiting, hyperacidity, hypersecretion and in rare cases, cardiospasm. The colic itself is simply a paroxysmal discharge of this state of irritation. Lead resembles in its action pilocarpin as shown in Westphal's experiments, when by injection of this substance he produced

vagus irritation with spastic ischemia of the intestinal tract and resulting necroses. Indeed lead prepares the ground for neurogenic ulcers as does no other agent. The action is central, but it is aided by a peripheral neuritis of the vagus.

Schiff holds that typical colic with its single attacks of intense pain is not nearly so common as are symptoms of prolonged or chronic disturbance, recurrent attacks of pain lasting for months perhaps, sometimes coming on daily at the same hour, remitting for a while, then recurring in the same way. Often the pain is related to certain foods as in gastric ulcer or to fasting as in duodenal ulcer. Especially common is pain at night followed by acid vomiting in the morning. Of the 48 cases which he studied 14 proved to have indubitable ulcer, 10 had symptoms typical of duodenal ulcer, 1 had cardiospasm, 16 had severe gastralgia with high grade hyperacidity and hypersecretion and 7 had symptons suggestive of ulcer but without secretory irritation.

Cushing's theory (personal communication) was that lead causes inflammation of the parasympathetic nervous system which controls gastric secretion and motility.

Teleky in 1929 reported a case of gastric ulcer in a zinc smelter, who had a history of frequent attacks of colic; also a case in which a severe colic apparently was the cause of the lighting up of an old gastric ulcer. Adler of Vienna reported that same year 4 cases of plumbism complicated with duodenal ulcer and a fatal case of colic with bloody vomit in a man who had had many attacks of lead colic. The autopsy in this case showed a ruptured gastric ulcer, and the rupture was attributed to the spasmodic contractions of the stomach under the action of the lead. Glaser[89b], Gutzeit[108a] and Koelsch[166a] all hold that peptic ulcer may be caused by lead.

However Czépai[47a], chief diagnostician of the Hungarian Social Insurance Institute, was unable to find any connection between plumbism and gastric ulcer. The frequency of gastric ulcer among 8,975 workers was 17.9 per cent., among 450 lead workers it was only 8.8 per cent. He believes that the statements quoted above were based on too small a number of observations.

Finally there are those who hold lead responsible for multiple sclerosis. Cone, Russel and Harwood[43a] suggest it as a possible causative factor in the remitting and exacerbating type of this disorder. In 6 cases of this type they found lead in stools, urine and cerebrospinal fluid. There was lead in the spinal cord at autopsy in a typical case of multiple sclerosis, and in the brain and cord of a case of neuromyelitis optica. Calcium therapy was found to be of distinct value. Bosches[17b] the following year discussed this theory and dismissed it, holding that there is no adequate proof for it and ample evidence against it.

Two recently published studies of lead deserve mention. Byers and Lord[30a] present evidence showing that lead poisoning in childhood has a decided effect on mental development. They made a follow-up study of 20 school children, who

had been in hospital for lead poisoning in infancy or early childhood. There was no marked encephalopathy, and all were discharged as recovered. The school records showed that only one had made satisfactory progress in school; the others had behavior difficulties, loss of normal inhibitions, were unreliable, cruel, impulsive. Three had recurrent convulsions, one had a positive Babinski reaction, another, hyperactive reflexes and sustained ankle clonus after 6 years.

Riggs and his colleagues[261a] found a significantly higher concentration of lead in the kidney and the pituitary gland in autopsies on 95 patients whose death was not adequately explained by clinical or necropsy findings as compared with 40 autopsies on patients with clearly defined causes of death. In the first group of these patients neuropathy as the chief cause of illness, repeated vomiting, peripheral collapse and elevated blood pressure without organic substrata occurred with significantly greater frequency than in the second group.

Mercury

Industrial poisoning from mercury and its compounds differs from accidental or suicidal poisoning by bichloride of mercury or the poisoning that follows mercurial inunctions. One does not look for severe abdominal symptoms and nephritis but for three characteristic symptoms, inflammation of the gums with salivation, muscular tremors and a form of nervous shyness which Kussmaul[175] called erethism. Usually the first thing noted is pain when chewing and excessive flow of saliva. The gums swell, bleed readily; the teeth loosen and may drop out. In severe cases there is not only pyorrhea but ulcers in the mouth and on the lips. In slow chronic poisoning there may be no salivation and no marked inflammation, only a complaint of dryness of the mouth and throat.

In the fairly rapidly developing cases stomatitis may be the only symptom noted, but usually muscular tremors also are present. These affect at first only the small muscles, those of face, tongue and fingers, and are seen easily, when the tongue is protruded, and when the hand is stretched out with the fingers separated and extended. It is an intention tremor increasing with the effort to control it, and it often happens that a man with this form of poisoning may be able to keep on with the accustomed movements required by his daily work, when it is almost impossible for him to perform a more unusual action, such as raising a glass of water to his lips. The tremors may affect other muscles, and in more advanced cases there are also violent jerking movements making work impossible and making the victim as helpless as a baby. Yet even in these severe cases the movements may die down altogether, if the man is quiet and feels himself free from observation. This does not mean that the palsy is hysterical in character; it is a part of the peculiar psychosis of mercurialism. Kussmaul's erethism is a form of nervous shyness and shrinking with loss of confidence, vague fears, inability to perform even the simplest act under observation. Sometimes there is great irritability with outbursts of anger on trivial provocation, in other cases drowsiness and apathy. Poor sleep also is common with despondency and loss of memory in the severer cases. L. I. Harris[127] in his investigation of New York hatters found that some of them would throw down their tools when he paused beside them and declare that they could not work if anybody watched them. Teleky[312] gives some striking cases of this kind of psychosis. Fellinger and Schweitzer[73] claim that endarteritis followed by gangrene of the toes or feet was a sequel of mercury poisoning in three workmen (see Part II).

In the United States the most serious cases of industrial mercurialism occur in the metallurgy of cinnabar, mercury sulphide, which is itself harmless[48], in making thermometers and like instruments, in laboratory work[287], in the use of mercury solder, repair jobs with the acetylene torch, in short any job which re-

quires the application of heat (Williams and Schram[336]). A new source of mercury poisoning is its use in antifouling paint[92].

A much slower form is seen in the felt hat industry, where for centuries mercurialism has been notorious, as witness the expression in England, " as mad as a hatter ", in the United States, " Danbury shakes ". As a usual thing the felt hat industry does not give rise to serious forms of mercurialism, for the exposure to mercury is not great in most plants. This industry is responsible for much the largest number of cases in all industrial countries, but the form usually is slow and mild. Mercuric nitrate is used in the process known as " carrotting " the fur of rabbits, beavers and muskrats in order to make the scales of the hair separate from the cylinder and to soften and twist the cylinder, thus increasing the capacity of the fur to felt, that is, to form a closely tangled mat. Most of the mercury is given off from the carrotted fur during the various processes the felt undergoes.

Several examinations of groups of workers in the hatter's trade have been made in the United States. L. I. Harris[127] in 1912 found 40 incontestable and 20 probable cases of mercurialism among 212 hatters' furriers in New York. In 1922 Wade Wright[349] examined 108 hatters and hatters' furriers in Danbury, Connecticut, and found that 53 showed at least two of the three classic symptoms. Two studies were made by the United States Public Health Service and published in 1937 and 1941[233,234], the first covering fur cutters, the second felt hatters. Fifty-nine cases of chronic mercurialism were found among 534 hatters. They had worked in air containing from 2.1 to 5.0 mgm. of mercury per 10 cubic meters of air, and the incidence of mercurialism was seen to increase with the increasing amount and duration of exposure, if the latter ran above 1.0 mgm. per cubic meter of air. As a result of this investigation it was possible for the Federal and the Connecticut health authorities to bring about a voluntary abandonment of mercurial carrot on the part of the felt hat manufacturers, thus making safe what has been for centuries a dangerous trade. At a conference, called by the Public Health Service in Washington on May 19, 1941, of manufacturers' and labor organizations, a resolution to become effective December 1st, 1941 was passed unanimously. It prohibited the use of mercurial carrot in the preparation of hatters' fur or the use of such fur in the manufacture of hats.

Organic compounds of mercury have been used extensively in England since 1914 as fungicides, most often the dimethyl compound. Hunter and his colleagues[146] describe four cases which originated in a factory producing fungicides. The symptoms were not those of poisoning by inorganic mercury except the tremor, for the nervous system alone was affected. There was ataxia, dysarthria and gross constriction of the visual fields but no changes in memory or intelligence. In rats the peripheral nerves and posterior spinal roots were affected first, later the middle lobe of the cerebellum.

Atkinson[4] has adanced a new test for the diagnosis of mercurialism, namely a brownish colored reflex from the anterior capsule of the lens. He found it in 37 of 71 men who had been exposed to mercury. Of these, 14 showed symptoms of mercurialism, and in all the colored reflex was present.

Mercury fulminate is a skin irritant, but systemic poisoning from absorption is very rare, though occasionally there may be a mercurial salivation. Some very unusual cases were reported recently from France, cases of acute edema of the face with spasmodic coryza, anaphylactic in character, in four newly employed men. There was also a fall in blood pressure, leucopenia and albuminuria. There were also two cases of " gassing " with loss of consciousness, probably from ethyl nitrite which is given off in the production of fulminate.

For metallic mercury the maximum allowable concentration should be 1 mgm. per 10 cu. meter according to the American Standards Association.

Manganese

The literature on this rare and clearly characterized form of industrial poisoning was reviewed by Edsall and Drinker in 1919, when 15 cases had been described in Germany and France among workers exposed to dust containing manganese as oxides and silicates and 9 (Casamajor[36]) in the United States. The cases seen by Edsall, Wilbur and Drinker[64] brought the number in America up to 39. Two more were reported by Davis and Huey[50] in 1924 and 6 by Gaylé[86] in 1925. Since then reports from Europe and America have swelled the number, and by 1937 McNally[213] had collected 131 cases from the literature.

Edsall and Drinker give the following list of symptoms, in the order of their appearance: a history of work in manganese dust for at least three months; languor and sleepiness; muscular twitchings from fine tremors to gross rhythmical movements of limbs, trunk and head; cramps and stiffness in the calves, especially at night; slight increase in tendon reflexes; ankle and patellar clonus; retropulsion and propulsion; peculiar slapping gait; occasionally uncontrollable laughter; less often weeping; absence of sensory, gastrointestinal, eye and genitourinary disturbances; negative blood, urine and spinal fluid findings. The prognosis is hopeless as to recovery but favorable as to life.

The diagnosis of manganese poisoning is not easy; indeed in the absence of a history of exposure probably it would prove impossible. Isolated cases probably escape detection as industrial in origin. Gürtner says that the symptoms may simulate progressive bulbar paralysis, amyotrophic lateral sclerosis, postencephalitic Parkinsonism, multiple sclerosis, progressive lenticular degeneration (Wilson's disease), and only a history of exposure will clear up the puzzle.

Flinn, Neal and Fulton[79] investigated an outbreak in a Pennsylvania ore-

crushing plant. They estimated the particles of dust in the air and made exhaustive examinations of 34 men exposed to ore dust. Eleven were found to have manganese poisoning, 8 of them incapacitated at the time. The picture given corresponds to that described by Edsall and Drinker, but in addition a leucopenia was noted especially in the advanced cases.

The average exposure to manganese in the air was 40 mgm. per cubic meter, the highest was 173 mgm. The lowest average concentration at which chronic poisoning was found to have occurred was 30 mgm. per cubic meter.

Several experimenters have succeeded in producing symptoms and lesions resembling those of manganese poisoning in man[217]. Canavan, Cobb and Drinker[32] made a very complete study of the pathological changes in the body of an old manganese worker, who died of cardiorenal disease at the age of 69 after about 14 years of disability from manganese poisoning. There was atrophy of the brain, which showed most strikingly on frontal section, for the lateral ventricles were dilated and the basal ganglia so shrunken as to distort the anatomical outlines. It was in these ganglia that the significant pathological process was found, degeneration of nerve cells with gliosis, which affected the caudate nucleus, the putamen, the globus pallidus and the thalamus, the last most severely.

A curious autopsy report comes from Germany. Voss[321] describes the findings in the body of a man with manganese poisoning who died of bronchopneumonia. He found no changes in the basal ganglia, only in the right pyramidal tract and in the fibres of both sciatic nerves. The principal use of manganese is in the iron, steel and alloy industries. A much less important use is in the making of dry cell batteries. The ore comes chiefly from Russia, India, Brazil, but there are deposits in the United States and the wartime demand is leading to their exploitation. The breathing of dust-laden air in mines and mills is the way in which industrial poisoning occurs, and usually it is a slowly cumulative action, taking a year or more to develop, but cases have been known to follow as little as three months' exposure. Lately a new source of manganese poisoning has come to light, namely the fumes from welding manganese alloys.

The American Standards Association has adopted 60 mgm. per 10 cu. meter of air as the maximum allowable concentration of manganese.

Metal Fume Fever

Brass founders' ague, spelter shakes, brass chills, one of the oldest forms of industrial disease in the brass and zinc industries, now is included under the term "metal fume fever", together with a similar symptom complex, which follows exposure to superheated copper[124], to magnesium oxide[56] and to other metals. Brass is an alloy of copper and zinc, and there was for many years a

controversy as to which element was responsible for the ague-like attack so familiar to brass founders. Although as early as 1831 Thakrah attributed the illness to the oxide of freshly burned zinc, Lehmann in 1910[185] settled the question definitely by producing in himself and four others typical brass chills from breathing the fumes of burning zinc, and he isolated zinc from the urine. These results have been confirmed repeatedly. Guelman[108] found glycosuria caused by disturbed glycogen metabolism in 8 out of 28 cases of brass founders' ague, and in 13 of the 15 men examined for blood sugar he found an increase.

Zinc oxide is not toxic, but neither is the illness produced by brass fumes typical of a metallic intoxication; it resembles, as Lehmann pointed out, an acute infection, and it is followed by a certain degree of immunity. Lehmann's explanation of the pathology still is the accepted one. The particles of oxide are inhaled, they spread over the surface of the alveoli of the lungs, where they exert a destructive action on the epithelial cells, and it is the absorption of proteids from these dead cells that produces the malaise, chill, fever, leucocytosis, etc. The reason why the illness cannot be brought on by breathing ordinary zinc oxide powder, according to Philip Drinker[56], is that the latter consists of large agglomerations of oxide particles, while the freshly sublimed particles are small and very dry, passing easily through the bronchioles.

The same clinical picture was produced by Drinker and his associates[56] with freshly sublimed magnesium oxide. Koelsch[166] saw typical ague in men rolling red-hot copper ingots and Hanson[124] in men melting copper in an electric furnace. The reason why brass workers suffer most is that zinc melts at a much lower temperature than does copper, and therefore, in making the alloy zinc fumes are produced in abundance long before the copper is melted. Other industries, which give rise to zinc oxide chills, are bronzing, zinc smelting, zinc coating (galvanizing), autogenous welding of zinc or galvanized iron and working up dross from galvanizing tubs.

It is a question whether there is a chronic form of metal fume fever, but there can be no question of an accumulation of effects, if the attacks are very frequent. Brass founding is not a healthful occupation (Guelman[108]), but in all cases of chronic illness in these men it is well to look for lead. Both brass and so-called railway bronze may contain as much as 9 per cent. of lead which volatilizes with the zinc and causes typical plumbism (Pedley and Ward[249]).

Cadmium

Cadmium, which was for long a rare metal in industry, of late has become very important as an ingredient of alloys and in electroplating. Exposure, therefore, comes in the smelting of ore[148], making alloys, electroplating, making and

spraying pigments and in welding metal when the metal or the welding rod contains cadmium.

Industrial poisoning from cadmium was a medical curiosity as late as 1932, when Prodan[262] published his valuable experimental studies. It is still a rare finding, but that may be because cases have gone unrecognized, and since the use of the metal is increasing rapidly, physicians doubtless will become more familiar with the picture of its physiological action. Striking cases in the earlier literature were decribed by Sovet (Prodan), by Legge[181] and Schwarz[281]. Sovet's 3 cases were acute, with gastrointestinal disturbances, profound prostration and oliguria with tenesmus. The others, chronic, had involvement of the lungs, dark urine and gastrointestinal inflammation.

The recent literature yields several illustrative cases. Nasatir[252] of the National Institute of Health reports a fatal case. Death occurred on the fifth day after exposure to cadmium fumes caused by burning off with an oxyacetylene flame deposits of metal containing a high percentage of cadmium. The clinical symptoms consisted of an increasing feeling of constriction of the chest and increasing dyspnea and cough which became extreme before death.

A brief report of one industrial case and mention of a second comes from the Ohio Industrial Hygiene Bulletin, 1939. The poisoning resulted from accidental overheating of cadmium. The victim suffered from weakness, dyspnea, pain in the chest, paroxysms of coughing and profuse sweating. There were moderate fever and moist râles over the lungs, no other symptoms.

Bulmer, Rothwell and Frankish[26] reported in 1938 15 cases with 2 deaths. Postmortem examination revealed congestion of the lungs with edema, hemorrhage and partial collapse. The cells of liver and kidneys showed cloudy swelling.

It is evident that in man as in Prodan's experimental animals the action of cadmium fumes and dust is chiefly on the lungs; other effects are far less important. The symptoms resemble those of nitrous fume poisoning. A case seen by one of us (R.T.J.) was very characteristic. This was in a young Mexican laborer, who was sent to the hospital as a case of metal fume fever following the use of an acetylene torch on the inside walls of a furnace in which cadmium residues had been recovered from scrap metal. He was extremely ill with severe dyspnea and exhaustion, and he gave a history of severe headache, constant coughing and chest pain, which came on soon after his job was over. His lungs were clear, but his respirations were 40, pulse 130, temperature 100° F. Oxygen administration failed to affect his respiratory rate but lessened the chest pain. The temperature rose to 104° F., pulse to 140 and respiration to 50, and the leucocyte count was 21,100 with 87 per cent. polynuclears. A patchy bronchopneumonia was revealed by x-ray. Nine days after exposure the pulse rate was 160 and respiration 70 and cyanosis was marked. Just before death a wide-

spread patchy pneumonia was evident. Blood and urine were essentially normal; Wassermann was negative. At autopsy the lungs were edematous and contained solid areas from which seropurulent fluid could be expressed. The cause of death was bronchopneumonia with edema. No significant change was found in any other organ.

The Indiana Bureau of Industrial Hygiene reported in 1943 2 cases of severe, acute, cadmium poisoning caused by the fumes from the use of a blow torch on cadmium-plated steel pipe. After four hours of this work both men were violently ill with vomiting, pains in the chest and difficult breathing. One recovered; the other died four days later " of a severe chest involvement ".

Cadmium poisoning has been reported also from eating acid-containing foods such as fruit juices left standing in cadmium plated cooking utensils or " ice-cube " trays.

The American Standards Association has adopted as the maximum allowable concentration of cadmium in the air, 1 mgm. per 10 cu. meters.

Beryllium

Up to 1938 the articles on beryllium or sometimes, glucinum poisoning as an occupational disease came almost entirely from Russia. Guelman summarized them that year for the I.L.O. Encyclopedia. Beryllium is a rare metal extracted from beryl, which is 14 per cent. beryllium oxide and is present in many silicates and phosphates. It is a very valuable addition to alloys, making them more resistant and harder, and its use has increased greatly during the present war. Dust in very fine division is the hazard in most processes, but in those that require great heat the metal itself is liberated. Hydrogen fluoride comes off much earlier, however.

The Russian publications show that it is not easy to separate the action of beryllium and its fluoride compounds from that of other fluorides. They observe an irritant action on skin, mucous membranes and conjunctiva, rarely serious in character. They also observe, in the extraction of beryllium by heat, symptoms of metal fume fever, but this is followed often in a few days by a pulmonary disorder, cough, reduction of chest expansion, numerous moist râles and an x-ray picture resembling miliary tuberculosis. Toward convalescence bronchioalveolitis appears and occasionally more or less pronounced pneumosclerotic changes.

Guelman tested the oxide and the oxyfluoride on animals and found the former to give rise to only slight damage, while the oxyfluoride set up a fatal, necrotic, fibrinous pneumonia. He concludes that the principal role in this form of occupational poisoning is played by beryllium, aggravated by fluorine.

Fairhall and his colleagues[71] as a result of exhaustive studies of the action of beryllium and its compounds, when administered to animals, conclude that beryllium is not of itself toxic, but that the fumes arising from the electrolysis of molten fluorides containing beryllium fluoride or oxyfluoride are decidedly toxic. Such salts of beryllium as the fluoride and sulphate, which hydrolyze easily, were found to have an irritant effect on the skin, but not the neutral salts. A comparison of the relative toxicities of beryllium, magnesium and zinc by intraperitoneal injection showed the first to be least, the last most toxic.

Since no consistent pathological change can be attributed to beryllium, " it appears that whatever toxicity has been found to occur with the beryllium salts is due to the toxicity of the acid radical such as the fluoride or oxyfluoride or to an objectionable condition brought about by the hydrolysis of certain of its salts, such as the chloride and sulphate. No safe permissible working standards should be based upon beryllium alone.[71] "

More information on this subject may be looked for soon, since studies are being carried on by several industrial companies as well as by the National Institute of Health.

Magnesium

Mention has already been made of the fact, confirmed by P. Drinker's experiments on man, that magnesium oxide[56], freshly formed, can set up metal fume fever. A much more serious injury from magnesium has come to light recently, chemical gas gangrene from metallic magnesium. This is a new form of industrial injury, which the extensive use of metallic magnesium has brought about. According to McCord and his colleagues[210] wounds, scratches or cuts, that are caused or contaminated by magnesium or its alloys, are especially prone to become severely inflamed with accompanying blebs, and these lesions are obstinate, lasting for months. They succeeded in producing in animals sizable gaseous tumors by injecting under the skin particles of magnesium or an alloy, but not with aluminum or manganese. Analysis of the gas showed H_2 2.2 per cent., CO_2 1.3 per cent., O_2 15.2 per cent., and the remaining 81.3 per cent. probably is N_2. The Bulletin of the British-Colonial Board of Health, 12.33.1942, calls this " a new kind of gas gangrene " and urges that all particles of magnesium be removed promptly from the wound.

Jarzynka[154], who has had a five year experience with magnesium metal in fabrication, has seen 73 major burns and insists that they differ in no respect from the usual second and third degree burns.

In magnesium foundries fumes of SO_2 and of fluorides may be present especially in pouring.

Vanadium

In 1911 Dutton[62] described vanadium poisoning as he had seen it in a plant where vanadium ore was ground and prepared for use in steel production. His patients suffered from anemia with evidences of destruction of red blood cells preceded by polycythemia and a high hemoglobin. Loss of appetite, pallor, emaciation followed; there were albumen, casts and blood in the urine; diarrhea or constipation, cough, sometimes severe enough to cause hemorrhage, increased susceptibility to pulmonary tuberculosis, nervous disorders, hysteria, melancholia, dimness of vision occurred. Vanadium was found in urine, feces and saliva. This picture of widespread disorders has never been confirmed.

For many years thereafter little was added to this report of Dutton's. Then in 1939 Symanski[306] reviewed the literature, showed that it is only the pentoxide of vanadium, particularly in the readily absorbable form of dust, which is harmful to workers, and gave the results of his examination of 19 men. He observed severe, suppurating conjunctivitis, inflammation of the upper air passages with continuous coughing and profuse expectoration sometimes with bloody pharyngeal secretion, constriction and pain in the chest; more or less severe bronchitis, sonorous and sibilant râles, evidence in x-rays of chronic bronchitis are encountered. He saw no evidence of disturbance of the gastrointestinal tract or of the kidneys or of the central nervous system; no impairment of vision and no changes in the blood picture were seen.

On the basis of animal studies Malfino[196] says that vanadium anhydride is absorbed and is eliminated in the urine, where it can be demonstrated; it has a strongly irritant action on the respiratory tract.

Zinc

The commonest form of sickness caused by a compound of zinc is the so-called " brass founders' ague " from inhalation of freshly sublimed zinc oxide. This has been discussed under " metal fume fever ". Metallic zinc has been regarded as giving rise to chronic poisoning with gastric disturbances, even peptic ulcers (McCord[207]), but K. Drinker and her colleagues[12] found no acute or chronic illness attributable to zinc in 24 workmen, who had been exposed from 2 to 35 years. However, it must not be forgotten that commercial zinc usually contains arsenic and that " zinc white paint " may really be " leaded zinc " with 5 to 50 per cent. of sublimed white lead.

In a recent article Gocher[91] insists that, if men work in the fumes or dust of zinc oxide or chromate or sulphate as well as the chloride, they develop dermatitis, boils, conjunctivitis, gastrointestinal disturbances and anemia, provided the

exposure has lasted as long as six months. He gives blood counts, which differ little from the average for industrial workers, an increase of large mononuclears at the expense of the small mononuclears and of the polynuclears, a slight increase in eosinophiles.

Zinc chloride is used as a solder flux and as a preservative of wood. It is decidedly caustic. McCord and Kilker[207] reported 17 cases of severe skin lesions caused by handling wood impregnated with zinc chloride.

Antimony

Antimony has extensive use as a constituent of lead-antimonial alloy, especially for printers' type and storage battery grids; it is used also as the "golden sulphide" in rubber compounding, and exposure takes place in mining and smelting. In most of these occupations lead also is present, and the cases of intoxication that develop are almost always attributed to the latter, although some authorities have described what they consider to be uncomplicated antimony poisoning (Seitz[285], Schrumpf and Zabel[277]). Prosser White[329] says that occupational dermatoses from antimony are very rare. Quimby[263] has reported skin eruptions from antimony pentasulphide in rubber compounders. It is well to remember that commercial antimony usually is contaminated with arsenic.

Contrary to the usual opinion as to the relative harmlessness of antimony in industry is the assertion of Bradley and Frederick[20], who found in animals a damage to the heart muscle developing consistently as a result of administration of antimony compounds. They consider this metal more toxic than lead and urge electrocardiographic examination of exposed workers to determine the presence of damage to the heart.

Copper

As the sublimed oxide copper may be responsible for one form of metal fume fever. Irritation of the skin may be caused by blue stone, the sulphate, by finely divided copper and, according to Prosser White[329], by copper chloride, but the irritating effect of the dust in copper smelting must be attributed to the presence of arsenic (Dunlap[61]). Mallory[198] held the theory that chronic copper poisoning causes cirrhosis of the liver with hemochromatosis. A great majority of the cases he described were not connected with industry, but in four the work involved contact for many years with copper in some form. In these no cirrhosis of the liver was found, but moderate amounts of hemosiderin and hemofuscin were seen. Mallory's theory has not been confirmed by later investigation in this field.

Nickel

Nickel electroplating involves contact with the sulphate and chloride, and in susceptible persons these salts produce obstinate eczema. Nickel carbonyl, a gas, which is essential to the Mond process of producing pure nickel, has caused severe poisoning in England and in Germany. Up to 1934 47 cases with 1 death had been reported by the British Factory Inspection Service. It is said to be five times as toxic as carbon monoxide, being deposited over the surface of the pulmonary epithelium, which suffers severe damage, and passing out unchanged to the circulating blood. Fatty degeneration occurs in the vessel walls[3,21].

A strange and hitherto unexplained action of nickel, if indeed it is to be attributed to nickel, is described in the yearly report of the British Factory Inspection Service for 1933. Fourteen cases of industrial cancer had occurred in a nickel refinery, of which 13 were fatal.

Nickel together with cinnamon apparently was the causative agent in a case of dry, scaly, hyperkeratotic dermatitis in a baker (R.T.J.).

Silver

This is another of many formerly unimportant industrial substances, which the exigencies of the present war have brought into more or less prominence. Silver can be used as a coating for steel in aviation bearings, in telephone and telegraph instruments and bus bars and for lining tanks and pipes in food processing. Argyria, a bluish black deposit in the skin of metallic silver, apparently is the only lesion produced by silver. It is localized usually in those areas of the skin which have come in contact with silver. Generalized argyria follows absorption by mouth or by the air passages. Teleky[308] has described this form. Hill and Pillsbury[138] found in the literature 12 cases of localized and 8 of generalized argyria, all of industrial origin. The condition appears slowly, taking from 2 to 25 years or even longer. There may be pigmentation of the lining of the mouth. Argyria, local or generalized from prolonged application or ingestion of silver-containing medicaments, was not very infrequent in the past but now has become infrequent.

Efforts to encourage elimination of the silver have failed, and local treatment is of dubious benefit (Heimann[132]).

Arsenic

Arsenic is distributed very widely in nature, being found in almost all sulphide ores, and since the greater part of our lead, iron, copper, antimony and

zinc ores are sulphides, it follows that these metals are very likely to carry arsenic as an impurity. Chamber sulphuric acid, commonly made by roasting iron pyrites, frequently is contaminated with arsenic, and the same may be true of the hydrochloric acid made from sulphuric acid. The more expensive form of sulphuric acid, known as contact acid, does not contain arsenic.

Arsenical poisoning in industry is caused by exposure to dust of solid compounds or to the gas, arseniuretted hydrogen or arsine. The latter is much the more serious. The solid compounds are white arsenic, As_2O_3, the acetoarsenite of copper or Paris green, lead arsenate and calcium arsenate. Industrially white arsenic is recovered by roasting and subliming arseniferous ores or subliming the flue and baghouse dust in smelters which work up such ores. In the lead smelters of Utah and Colorado and in the copper smelters of Montana mild arsenical poisoning is frequent, but serious cases are very rare.

Paris green and the two arsenates have a very large use as insecticides, and the danger in this use concerns not only the makers of the compounds but the sprayers. In England white arsenic is used, together with sulphur and caustic soda or potash, for a sheep dip, and similar mixtures are used to preserve hides and skins of birds and animals. Arsenical poisoning has occurred in Germany among men handling hides from South America, which have been treated with arsenic, and there have been cases in England among men unpacking bird skins. W. Gilman Thompson[316] reported a case of arsenical poisoning with peripheral neuritis in a tannery worker and quotes a chemist as having found arsenic in 11 out of 42 samples of furs. Hayhurst[130] found it as an ingredient of glass, one Ohio glass factory using as much as two tons of white arsenic in a month.

The poisoning that results from exposure to arsenic dust usually is local, very rarely systemic. Skin lesions of various kinds, dermatitis, eczema, ulcers, scleroderma, bronzing, trophic changes in the nails, loss of hair, inflammation and ulceration of the mucous membranes and eyelids, are the commonest results of contact with arsenical dusts. Thickening of the skin of the palms may be the first symptom noted (Ayres[7]). Delicate parts of the skin such as the lips or eyelids, where mucous membrane and skin merge, are especially sensitive; so are the parts that are kept moist and warm as the scrotum and the axilla. A chronic inflammation with slow, painless ulceration of the mucous membrane of the nose, which results in perforation of the septum, is according to Dunlap[61] of the Anaconda Copper Company a very common accident in arsenic workers. It causes little suffering and does not result in deformity, for the bony part of the septum and the base are not involved. Dryness of the throat, cough and hoarseness are characteristic of arsenic workers.

In poisoning with lead arsenate the symptoms are more likely to be those of lead than those of arsenic. This is a fact well known to men engaged in pro-

ducing this insecticide, and among the reported cases lead is accused more often as the cause than is arsenic. Aub[5] saw a case of double wrist drop of 12 years' duration with difficulty in walking for 3 years in a man, who had used lead arsenate spray in forestry work for 27 years. On the other hand Kraetzer[173] reported a case of Raynaud's disease in a patient with typical symptoms of arsenical poisoning, contracted by prolonged use of arsenical insecticide in a greenhouse. Arsenic was demonstrated in the urine. In one case reported by the British Factory Inspection Service for 1933 the lesions pointed to arsenic, not lead; but in a second the reverse was true.

Fairhall and Miller[70] studied for 2 years the effect on rats of the arsenates of lead and calcium and the carbonate of lead. Most of the kidney damage was caused by the lead; blood destruction was greatest with the two arsenates. There was less storage of lead in the soft tissues than of arsenic. In the bones there was more storage of lead carbonate than lead arsenate, the arsenate radical apparently decreasing lead absorption or increasing its excretion.

W. Frohn[85] in 1938 published a report of arsenical poisoning in the vineyards along the Mosel, where the vines are sprayed, and the vintners also use the skins from the winepress to make wine for themselves. The symptoms were lesions of the skin and mucous membranes.

The picture of generalized, arsenical poisoning from solid arsenic, as seen in exceptional cases in industry, rarely is severe. Neuralgic pains and multiple neuritis with motor palsy, slight in degree, are characteristic of these cases. The palsy is likely to affect the long extensors of fingers and toes, as does lead, but it is distinguished from the latter by the severe neuralgic pains and by the tendency toward a multiple, symmetrical neuritis. A very rare form of industrial poisoning involving the optic nerve was described by Moleen[224], who saw a case of skin lesions and double optic atrophy in a man using arsenical insecticides.

Of 135 cases of poisoning by solid compounds of arsenic, discussed by Legge[182], 38 had gastric symptoms, 13 had tremors or muscular cramps, 6 had peripheral neuritis; of the remainder all had lesions of the skin, in 6 of which there were keratoses or epithelioma. He speaks of 3 cases of epileptiform seizures, a most unusual manifestation of such poisoning. The carcinogenic action of arsenic has been recognized since the famous pronouncement of Jonathan Hutchinson, and each year one or more cases of arsenical cancer of the skin are reported by the British medical inspectors of factories. Usually white arsenic is the agent, but recently there was a case of fatal epithelioma beginning in the axilla, which was ascribed to exposure to dust of acetoarsenite of copper.

Arsine or Hydrogen Arsenide. — Much more dangerous is poisoning by the gas, arsine or hydrogen arsenide. This is a subtle and powerful poison with a rapid characteristic action, but since it is always a result of accidental exposure,

since arsine has no use in industry, and caused by arsenic, which is not known to be present, the cases often escape detection. The gas may be given off in any process, which requires contact between dilute sulphuric or hydrochloric acid and a metal, usually iron, lead, zinc or antimony, and since there is a large number of processes in which such contact occurs, there are many possibilities for the formation of arsine, for it is only necessary that metal or acid be contaminated with arsenic. The essential factors are arsenic and nascent hydrogen, the conditions necessary for Marsh's test. Such an accident may occur in so many different kinds of industries that Wignall[330] suggests a search for hydrogen arsenide fumes in all cases where a mysterious form of illness shows itself among the workers; at least the question should be faced, whether there is any process which could possibly result in the production of these fumes.

The symptoms of this form of arsenical poisoning are those of a powerful hemolytic agent. They appear after an interval, sometimes a few hours, sometimes a day or two, according to the size of the dose, and are characterized by anoxemia, nausea, vomiting, pain in the epigastrium, headache, dizziness. The urine is dark, from the color of tea in mild cases to a Burgundy red in the more serious. Albumen and casts appear later, and in serious cases the urine becomes scanty with complete suppression in fatal cases. Somewhat later than the changed color of the urine jaundice appears with pain and tenderness in the liver region. It is a hematogenous jaundice from the destruction of red corpuscles and the accumulation of pigment in the circulating blood. A blood count shows anemia, sometimes very marked, and usually a proportionate fall in the hemoglobin, or the color index may be low. If the case goes on to recovery, the urine regains its normal color, but albumen may persist for some days, and long after the acute symptoms have disappeared the anemia still is demonstrable. Wignall[330] has found arsenic in the urine eight weeks after the accident. In fatal cases the man may pass into a typhoid state with delirium followed by coma, and there may be a general bronzing of the skin. Hemorrhagic nephritis and hemorrhagic inflammation of the liver are found at autopsy. The mortality in industrial cases is something over 36 per cent. (Glaister[89]).

One of the commonest sources of arsine is the cleaning of the sludge from tank cars or storage tanks which have held sulphuric acid, after they have been emptied and flushed with water[191]. Strong acid does not attack the metal, but dilute acid does, and if there is arsenic in either acid or metal, the dilution with the wash water allows the acid to attack the metal, liberating nascent hydrogen. Other sources are the spontaneous decomposition of ferrosilicon, the use of a galvanized zinc-coated pail in dipping out acid sludge, producing hydrogen for filling toy balloons by treating zinc dust with hydrochloric acid, reduction of nitro compounds to amino in dye works, acid pickling of arsenic-contaminated

metals[295], cyanide process for recovering gold and silver, work in chemical laboratories, the last probably the most important of all.

The latest source of arsine in industry seems to be cadmium production from zinc-cadmium ore which carries arsenic. Acid is used in the leaching of the finely ground ore, and cases of arsine poisoning have occurred.

Selenium and Tellurium

Selenium and tellurium often occur together as in electrolytic tank sludge and have much the same physiological action, with this difference, tellurium inhibits sweat, selenium does not. Both cause a garlic odor to the breath before any symptoms of poisoning have occurred. Selenium is used chiefly in glass and pottery manufacture, also as a catalyst and in making photo-electric cells. Tellurium has assumed importance during the war, for it can be used to strengthen steel[288]. Mead and Gies[215], examining men engaged in recovering pure lead, copper and zinc by electrolysis, found symptoms such as these to be common; dryness of the mouth with metallic taste, scaly, itching skin, anorexia, nausea, vomiting, somnolence. Drowsiness and apathy they found to be the most striking symptom.

Halter[114] described a case of industrial selenium poisoning in a paint mixer, who had severe skin lesions, edematous erythema on the exposed surfaces, enlargement of the liver, porphyrinuria. Selenium was detectable in the urine.

A case of poisoning by hydrogen selenide in a chemist engaged in its production has been reported from Germany[186]. Aside from the garlic breath the symptoms consisted in lacrymation, coryza, hoarseness, dyspnea, a purple rash on both cheeks and abundant moist râles over both lungs. The last subsided slowly; the rash lasted 10 days. Dyspnea and cyanosis continued, and thrombophlebitis in the right calf developed on the 22nd day. On the 52nd day the electrocardiogram revealed a definite lesion of the heart. Selenium could not be found in measurable amount in the urine.

Phosphorus

Phosphorus, once the most dreaded and spectacular of the industrial poisons, is now almost negligible. The effects of phosphorus poisoning in match makers were so visible and so distressing to see that the sympathies of the public were enlisted readily in the efforts to combat it and after all forms of governmental regulation had been tried, and it had been proved that the only way to put a stop to phosphorus poisoning was to abolish the use of white phosphorus in the making of lucifer matches, the principal civilized countries adopted this very

radical procedure, and now the making and sale of white phosphorus matches is carried on only in the Orient[117].

White phosphorus, lucifer matches were made first in 1833, and the disease known as " phossy jaw " was reported first by Lorinser of Vienna in 1845. Soon after that, cases were discovered in practically all European countries and in the United States. The reason for the widespread attention given to this form of occupational disease is not its great prevalence, for only a minority of those exposed suffer, 70 among 600 workers in Silesia in 20 years, 70 among 620 in 21 years in France, nor because it is so deadly, the mortality is from 2 to 20 per cent., nor because it is rapid and violent in its manifestation, for it is slow to an unusual degree, but because it is extremely painful; it attacks the bones of the jaw and results in great deformity, which is visible to everyone, and it is accompanied by a fetid discharge, which makes the victim a misery to himself and others. The essential factor in phosphorus poisoning is the action of the fumes on the periosteum, almost always of the maxillae, to which they gain access after removal of a tooth. Necrosis sets in and then a suppurative process caused by secondary infection through the pus organisms present in the mouth, then abscess formation, fistulae and the cachexia of chronic septicemia. Victims of " phossy jaw " in extreme cases die of this septic process; in slower cases they are likely to develop tuberculosis. Exceptionally the periosteum of other bones is attacked, and there may be fragilitas ossium.

The match now made is the safety match, for which amorphous, red phosphorus is used, and the " strike anywhere " match, made with the sesquisulphide of phosphorus, neither of these having the poisonous properties of white phosphorus. In a French match factory Nicolas and his colleagues[237] found that there was a great deal of skin disease from the handling of phosphorus sesquisulphide. It was a rapidly developing erythema with formation of vesicles or pustules and accompanied by severe subjective sensations and sometimes, by conjunctivitis. Greasy skins were most susceptible. They produced in volunteers an eruption with the paste and also with the powder. A wash of potassium permanganate and sodium bicarbonate caused prompt recovery.

Cases of phosphorus poisoning, however, have been reported from other industries, chiefly the production of phosphorus, in the chemical industry, in the manufacture of phosphor bronze and in making lights for miners' lamps. In Great Britain most of the cases of phosphorus necrosis coming to the knowledge of the factory Inspection Department have occurred in the production of phosphorus.

A sudden and unexpected reappearance of severe phosphorus necrosis took place in the United States in 1923–26, when a new kind of fireworks was manufactured in three factories on the Atlantic seaboard with the use of white phos-

phorus. The management was ignorant and reckless, and as a result 14 workers, all but 1 being women, had developed extensive necrosis of the jaw, and 2 had died of septicemia. The period of exposure was short, only 6 months in 1 case. So far as is known, this kind of fireworks no longer is made (Ward[323]).

Phosphorretted hydrogen, phosphine, PH_3, sometimes is encountered in the production of acetylene and also in the use of an acetylene torch supplied with impure gas. It is found also in the decomposition of ferrosilicon (see AsH_3) under the influence of moisture (Brezina and Teleky[22]). It is excessively toxic, resembling arsine in its action except that it is not hemolytic (Baader[9]). Carlisle[33] in an article on pulmonary edema in war plants mentions among the "noxious agents" which may cause such a condition, phosphorus oxychloride, trichloride and pentachloride.

Cyanides

Cyanides, sodium and potassium, are used on a large scale in industry especially in electroplating, cleaning and coating silver, case-hardening steel and iron and tanning, and as fertilizer calcium cyanide is used. Another important use is the production of hydrogen cyanide for the fumigation of ships and dwellings and the destruction of plant parasites.

These are asphyxiant poisons with a direct toxic action on the body cells retarding or stopping oxidation. Yet in spite of their dangerous character they are used in enormous quantities in industry and with apparent recklessness without any demonstrable harm to the users. We have been in automobile factories, where piles of sodium cyanide lay on the floor near the case-hardening furnaces and were shovelled into the furnace like so much coal, yet nobody had ever heard of any harm coming from it. Acute poisoning from cyanides does occur from time to time, but it is very rare. One of us (R.T.J.) was told of an accidental poisoning by cyanide dust involving 3 sprayers of insecticide, 1 of whom was found dead, the other 2, unconscious.

Chronic cyanide poisoning is an even greater rarity, though cases have been reported[117].

Acrylonitrile or *vinyl cyanide*, ($CH_2CHCNCOOH$), is a new industrial compound, important in the production of synthetic rubber. Tested by the Public Health Service[59], it was found to resemble hydrocyanic acid very closely in its toxic action. On the basis of its cyanide content the Service has suggested 20 parts per million as the maximum allowable concentration for acrylonitrile. These investigators have devised a test for the early detection of absorption, which depends on an increase of thiocyanate in the urine and in the blood stream.

Acrylonitrile, like hydrocyanic acid, renders the tissue cells incapable of oxy-

gen absorption, because an enzyme, which presumably makes this possible, has been destroyed. Animals vary greatly in susceptibility to it. These are the symptoms in man in the order of their appearance; flushing of the face, increased salivation, irritation of eyes and nose, respiration, at first rapid and deep, then shallow.

In animals the same sequence is found, and flaccid paralysis may follow, but it is transient. Severe convulsions may occur under heavy exposure yet not cause death. Administration of sodium nitrite doubles an animal's resistance, for it forms methemoglobin, which has an affinity for the nitrile molecule and removes it from the blood.

Wilson[339] has found that, in spite of elaborate precautions in synthetic rubber plants, mild exposure to acrylonitrile does sometimes happen and causes nausea, vomiting, weakness, occasionally headache and diarrhea. In several cases he saw mild jaundice, severe in one case and lasting four weeks. Usually the jaundice was accompanied by a low-grade anemia, 4,000,000, with leucocytosis of 12,000 but with a normal differential count. Urinanalysis was negative except for an increased bile content.

Industrial Solvents

These are the solvents used for natural gums, shellacs, resins, rubber, gutta percha; for the newer cellulose compounds, nitrate and acetate, used in making lacquers, dopes for fabrikoid, waterproofing, artificial leather, patent leather; for celluloid and nonshatterable glass; for fats, oils, greases, in degreasing machine parts and in dry cleaning and also as thinners for coatings and as removers of coatings.

The properties that govern the choice of a solvent are its ability to dissolve these substances more or less readily and its volatility, for it must evaporate fairly quickly to be practically useful. One other property is important, inflammability, for that influences insurance rates. This works to the detriment, fortunately, of one of the most dangerous solvents, coal tar benzene (benzol), but not to the detriment of the chlorinated hydrocarbons, which are being pushed actively, because they are not inflammable.

The solvents that are important to the toxicologist are avid for fats and volatile, their danger being in direct relation to these two characteristics. The more volatile the solvent, the quicker and more intense the contamination of the air in the workroom; the more avid for fat, the greater the affinity for the fats of the body, those of the blood and the central nervous system. This being true, it behoves physicians to look with suspicion on any new solvent, which is very efficient and a very quick drier.

Aliphatic or Petroleum Series of Solvents

Alcohols

Of the members of the aliphatic series used in industry, only the most important can be described. Methyl or wood alcohol was for many years a source of grave injury to industrial workers. Tyson and Schoenberg[319] estimated in 1915 that no less than 2,500,000 workers in the United States came in contact with wood alcohol in the course of their work, and they found about 100 cases of industrial poisoning caused by inhalation or skin contact. It was peculiarly an American poison. Up to 1906 the use of grain alcohol in industry was not lawful in the United States and denatured alcohol, so commonly used in Europe, was unknown in American industry; therefore methyl alcohol was the customary solvent, and all the prejudices of the practical man were in its favor. The striking cases of industrial poisoning, which served to bring about the change in legislation providing for revenue-free denatured alcohol, occurred in the varnishing of the interior of beer vats (Patillo[247], Casey Wood[346,347], Hale[112]) and in the stiffening of felt hats by means of wood alcohol shellac.

It is the effect on the eyes which makes methyl alcohol a poison to be specially dreaded. According to Lewin[189] there is no other industrial poison which has so sure and specific an action as the action of methyl alcohol on the optic nerve. Characteristically, the impairment of sight clears up partially for a period, giving hope of recovery, only to increase again and leave the victim blind in one or both eyes. DeSchweinitz[284] and Tyson[318] call it an optic neuritis, inflammation of the connective tissue of the optic nerve, which subsides but is followed later by atrophy. Holden[140] and Friedenwald[84] believe it is primarily a degeneration of the ganglion cells of the retina. Jeliffe[155] has reported two cases of multiple neuritis in painters using wood alcohol varnish.

A typical case, one rarely seen nowadays, came under the observation of one of us (R.T.J.). After working for three days cleaning a vat with a trade name product containing methanol, a workman became acutely sick, vomited, complained of gastric pains and blurred vision. He recovered quickly from all symptoms except the last. He is now almost totally blind.

The experience with bootleg liquor during prohibition in the United States made so profound an impression that methyl alcohol was almost driven out of industrial use and even now is regarded with an apprehension which it does not deserve. Sayers, Young and Schrenk[274] found that dogs suffered no injury to the optic nerve nor any other significant effect after being exposed 8 hours daily for 379 days to 450 to 500 parts per million. Four pups born during the experiment were normal.

The higher alcohols give no trouble in industrial use. Theoretically the toxicity of the alcohols rises as the series goes up. If one goes by the results of intravenous injections of animals with the members of this series one finds toxicity mounting, from methyl to ethyl, propyl, butyl, amyl. This is Richardson's law, but it is of no use to the industrial toxicologist, who does not go by intravenous injections but by the breathing of contaminated air. Alcohols above ethyl have too low a volatility to poison the air unless heat is used. Amyl alcohol, the most dangerous according to Richardson, is the least volatile, while methyl, the safest, according to him, is the most volatile, and it is the only one that practical experience has shown to be dangerous. That is, no case has been recorded in which one of the higher alcohols used alone was responsible for occupational poisoning, but there are cases of narcotic poisoning from mixed fumes containing one of the higher alcohols, and it may be that in combination with other narcotics they may play an important part.

Acetates

For the acetates experience seems to show that methyl acetate is the least narcotic but somewhat more irritating to the eyes and the upper air passages than the higher members of the group. It has been known to cause a tight feeling in the chest and breathlessness. Ethyl acetate is more narcotic than methyl, although Zangger[352] regards it as the safest of all the organic solvents. Normal and isopropyl acetates have given no trouble so far as is known. Normal butyl and amyl acetates are about the same in irritating and narcotic properties, but butyl is 25 per cent. more volatile than amyl. Both are more active than the lower acetates and may cause burning of eyes, nose, throat, cough, tightness in the chest, bronchial catarrh, headache and indigestion, as has been known for years. Many men and women can use it without even discomfort, and both German and British factory inspectors after careful study can find no constitutional disturbance traceable to butyl or amyl acetates although one fatal case in 1930 followed the use of a mixed solvent containing amyl acetate.

Acetones: Ketones

When one reads the literature on acetone, one finds much about its narcotic action, but here again it is a question of laboratory animals, not human users. Acetone has an innocent history so far as its industrial use is concerned. Kobert[164] said that it was almost inconceivable that poisoning could follow its use. Greenberg and his colleagues[102] investigating factories in New York State, where an acetone-methanol solvent was used in making "fused collars", found that the

air contained 40 to 45 parts per million of acetone. They examined 19 workers but, though acetone was found in the urine of all, no clinical symptoms nor blood changes were found.

Acetone is dimethyl ketone. Now there is also methylethyl ketone, called butanone, and methylpropyl ketone or pentanone. The Public Health Service has tested these and several others of the group and finds that all are narcotic, depressant to the body temperature, the respiratory and the heart rate; all abolish corneal, auditory and equilibratory reflexes, the action in the straight chain methyl ketones being proportional to the number of carbon atoms in the chain.

Aldehydes

Formaldehyde, acetaldehyde, croton aldehyde, paraldehyde and *allylaldehyde* or *acrolein* all are used in industry, but only the first and last are of importance. *Formaldehyde* is used in enormous quantities, especially in the production of plastics, of which bakelite is the best known. Workers exposed to the fumes suffer from local irritation of eyes, throat, nasal passages, skin, but an effect on the deeper air passages is seen rarely. There is, of course, a wide variation in individual susceptibility, and some men cannot work in an atmosphere quite tolerable to others. This is true both with regard to skin eruptions and inflammation of eyes and mucous membranes. Cases have been reported of keratitis, corneal ulcers, dimness of vision, painful skin lesions, bronchopneumonia, asthmatic attacks, even temporary insanity, all attributed to formaldehyde, but in all of them other chemicals were present, phenol, methyl alcohol, " hex ", turpentine, benzene. It is notoriously a strong sensitizing agent. Patch tests should not use even 5 per cent.

Acrolein is allylaldehyde, an extremely irritating gas, given off by the heat decomposition of fats. Lewin[190] and Iwanoff[152] found it more toxic than formaldehyde, and Koelsch[167] described two cases of poisoning, one fatal, in men using an oxyacetylene torch on the inside of a tank car which had contained rape seed oil. The commonest sources of this gas are melting old stereotype plates covered with oily ink and making soap and candles.

Glycols: Cellosolves: Dioxan

Glycols are assuming more and more importance as solvents for coatings, printing inks, plastics. They are diatomic alcohols containing two HO groups, and there is a long list of glycols and their derivatives, many of them industrially useful. They are not volatile at room temperature, and poisoning has occurred only when heat has been applied.

The glycol, which was used as a vehicle for the notorious sulfanilimide elixir, was diethylene glycol. In animal experiments, when administration is by mouth or under the skin, the glycols have the same action as had the elixir, namely, severe damage to the kidneys. In industrial use, where it is a case of breathing fumes, the picture is different, the symptoms pointing to an action on the central nervous system and the bone marrow. Chronic intoxication by glycols in animals has been studied by Morris, Nelson and Calvery[229], who found ethylene and diethylene glycol the most toxic, producing calcium oxalate stones in the kidneys. Propylene glycol apparently was harmless.

The best known members of the group are ethylene glycol monoethyl ether, known as *cellosolve,* and the monomethyl compound, *methyl cellosolve. Carbitol solvent* is diethylene glycol monoethyl ether. Cranch, Smyth and Carpenter[45] say it is less irritating to the skin than glycerine, less likely to set up cutaneous allergy. The ethylene glycols were tested by the Public Health Service[226]. Animals given a lethal dose showed congestion and edema of the lungs, congestion of the kidneys, petechial hemorrhages in the gastric mucosa. However, Greenburg[100] was able to declare in 1938 that no cases of industrial poisoning from the monoethyl compound, the cellosolve, had come to light, and this seems to be true in England also (Browning[23]), although it has been used extensively in spray painting.

Methyl cellosolve has a different history, perhaps because its use in industry has required the application of heat causing volatilization. It came into use as a solvent for the stiffening material used on shirt collars in the so-called "trubenizing" or "fusing" process. This requires pressing with a hot iron, while the ordinary uses of glycol solvents require no heat. In 1936 Donley[53] reported a case of toxic encephalopathy in a woman employed in a shirt factory pressing fused collars. In addition to the brain symptoms she had anemia, 3,500,000 red blood cells, hemoglobin 85 per cent., lymphocytes 46 per cent. The solvent contained methyl cellosolve but only 3 per cent.

Greenburg's[100,101] cases were more convincing, for the solvent to which they were exposed contained 33 per cent. methyl cellosolve. He reports an investigation of 19 young men employed in making fused collars, 2 of them acutely ill with severe anemia of the aplastic type, tremors, marked mental dullness, 1 with a history of multiple neuritis and abnormal neurological findings and 16 with abnormal blood pictures. In this last group there were 4 with abnormal reflexes and tremor of the hands and 4 with the above signs exaggerated and in addition, symptoms of drowsiness and fatigue. Greenburg advises careful blood examination for the detection of intoxication in an early stage. The picture is one suggestive of macrocytic anemia with reduction of platelets and the appearance of young granulocytes. It may be mistaken easily for benzene poisoning.

Diethylene dioxide or *dioxan,* the second ether of ethylene glycol, came into use as a solvent in the early thirties, and at first it was looked upon as comparatively safe. The Bureau of Mines[350] tested it in 1930 and found it of comparatively low toxicity but with a locally irritating action so intense as to provide ample warning at a point far below that at which serious harm would result. However, in actual practice such warnings are not always heeded, and in 1934 Barber[10] published the story of 5 fatal cases in workers who died after an acute illness lasting 5 to 8 days. They had inhaled fumes with greater content of the toxic substance than ever before because of a change in the apparatus and had suffered from smarting of nose and eyes, headache, drowsiness, dizziness, anorexia and nausea but had kept on working. Within a fortnight all were seriously ill with severe gastric symptoms, liver enlargement without jaundice, anuria and uremic coma. Autopsy on 4 of the 5 revealed hemorrhagic nephritis and necrosis of the liver.

Animal tests were made after this, and it was found that dioxan produces damage to liver and kidneys of guinea pigs, rats and rabbits. Wirth and Klimmer[343] say that it may produce paralysis, and damage to the blood forming organs also.

Studies made by the Public Health Service[239] on the effects of repeated exposures of rats to vapors of glycol ethers, 300 to 400 parts per million, show that " small but measurable effects " on the cellular elements of the blood appear, such as increase in young granulocytes, decrease in hemoglobin concentration and red cell count. They agree with Greenburg that examination of the blood will yield the earliest warning of poisoning.

Furfural

Furfural is about one third as toxic as formaldehyde, dose for dose, but practically it is far less harmful, since it is a fairly nonvolatile liquid, while the latter is a gas. Korenman and Resnick[171] found in a factory in Odessa, where the air contained from 0.007 to 0.053 mgm. per liter, that there was a complaint of red, weeping eyes, itching of the throat and headache. It is said to cause anaesthesia of the cornea.

Ether

Sulphuric ether is used in this country chiefly in the production of photographic films and of smokeless powder and military gun cotton. During World War I there were many cases of acute ether intoxication among the young women employed here and in England but never of a serious character. An interesting and thus far unexplained feature of this was a polycythemia with red counts

running from 5.5 to 7.8 million in over one half of those examined[222]. In Germany two severe cases of ether poisoning, one fatal, were caused by spilling ether in a factory making collodion films with ether-alcohol solvent[22].

Metol

Metol, which is methyl-p-amido-m-cresol sulphate, has been used for many years in photography, where it is notorious for producing eczematous or ulcerative lesions on the skin and eyelids.

Nitroglycerine

Nitroglycerine produces its well known effects on workmen who are new to the job, but the majority acquire a transient immunity to it. No form of chronic poisoning has ever been discovered among nitrators of glycerine or makers of dynamite and mixed powders (Ebright[63], Heitz[134]).

Oxalic Acid

Grolnick[105] has described a case of early gangrene of the fingers like that caused by phenol in a man who used oxalic acid at intervals for two years in floor cleaning. Howard's case[142] was one of inhalation of steam from hot oxalic acid in a man who cleaned automobile radiators by boiling them in a strong solution of the acid. There was inflammation of the nose, throat and air passages, nosebleed, obstinate cough, vomiting, bloody stools, gradual emaciation and increasing weakness. An intense pain in the back was the chief complaint, and there was albumen in the urine, but apparently no microscopic examination was made of either urine or blood.

Hexamethylenetetramine

Hexamethylenetetramine, also called " hexamine ", " hex " or " urotropin ", is an excellent accelerator for rubber vulcanization, but it is so markedly irritating to the skin of a large proportion of individuals that its use has been practically abandoned. No instance of the familiar action on the kidneys has ever been noted in industrial cases.

Acetylene

When an acetylene welder suffers an attack of " gassing ", the cause must be sought either in the metal he is welding or in some accidental impurity in the gas. According to Legge[183] 29 cases of gassing in connection with the use of

acetylene torches were notified between 1921 and 1931, 20 of them in welders, rivetters, etc., when possibly such substances as zinc oxide from galvanized iron or naphtha fumes from bituminous paint or carbon monoxide may have been the active agents. Nine cases were caused by acetylene gas leaks and were characterized by vertigo, headache, mild gastric symptoms, semiasphyxia, loss of consciousness for brief periods. The impurities that may be present in acetylene gas include phosphine, arsine, hydrogen sulphide, carbon disulphide and carbon monoxide. Impure acetylene may contain as much as 0.17 mgm. per liter of PH_3 and 0.25 mgm. per liter of H_2S according to Adler-Herzmark[1] who saw a case of jaundice with glycemia in an acetylene welder.

Chlorinated Hydrocarbons

These solvents, which are non-inflammable as well as strongly solvent, have a wide and increasing use as degreasers of metal, cleansers of textiles, solvents for rubber, tar and gums, thinners for cellulose lacquers and in treatment of garbage, tankage and bones. Other uses are the production of high grade lubricating oils from inferior stock, the production of edible and non-edible vegetable oils, the purification of explosives and for refrigeration.

The chlor compounds may be divided into three groups, namely, the saturated (paraffin) group, methane, etc.; the olefins, unsaturated ethylene, propylene, etc.; the naphthalenes. The following list includes those compounds which are of more or less importance in industry.

Saturated Compounds of the Methane Series

Common Name	*Chemical Name*	*Formula*
(1) Methyl chloride	Monochlormethane	CH_3Cl
(2) Chloroform	Trichlormethane	$CHCl_3$
(3) Carbon tetrachloride	Tetrachlormethane	CCl_4
(4) Ethyl chloride	Monochlorethane	C_2H_5Cl
(5) Ethylene dichloride	Dichlorethane	$C_2H_4Cl_2$
(6) Ethylene trichloride	Trichlorethane	$C_2H_3Cl_3$
(7) Acetylene tetrachloride	Tetrachlorethane	$C_2H_2Cl_4$

Unsaturated Compounds of the Methane Series

(8) Acetylene dichloride	Dichlorethylene	$C_2H_2Cl_2$
(9) Acetylene trichloride	Trichlorethylene	C_2HCl_3
(10) Tetrachlorethylene	Tetrachlorethylene	C_2Cl_4
(11) Halowax	Chlorinated Naphthalenes	$C_{10}H_5Cl_3$
	from Tri to Hexa	$C_{10}H_2Cl_6$

Of these, Nos. 1, 3, 5, 7, 9 and 11, are industrially the most important.

It is necessary that the common as well as the chemical names be known, for the former often are very misleading. The unsaturated group is less toxic than is the saturated group, and if we should go by the names commonly used in industry, we should class certain highly toxic compounds of the saturated group among the comparatively harmless unsaturated ones, as, for instance, tetrachlorethane, which is known as acetylene tetrachloride, or dichlorethane, known as ethylene dichloride.

As to the comparative toxicity of the members of the first group von Oettingen[240] says that the narcotic action increases with the number of chlorine atoms, but that data are not available concerning the connection between liver damage and the number of chlorine atoms. However, back in 1915 Evarts Graham[96] declared that experimental necrosis of the liver increased in animals with the increase of chlorine atoms, being brought about by a smaller dose of CCl_4 than of $CHCl_3$ and much smaller than that of CH_2Cl_2.

On the basis of animal experiments carried on till death came, Matruchot[203] gives the comparative toxicities as follows: trichlorethylene 1.0, per (tetra) chlorethylene 1.4, dichlorethylene 1.5, dichlorethane 1.6, carbon tetrachloride 2.6, chloroform 4.2, trichlorethane 5.0, tetrachlorethane 6.0.

The unsaturated group is highly narcotic but does not give rise to degenerative changes in the liver as do the members of the saturated group (Barrett and associates[11], Hammes[122]).

Henderson and Haggard[136] lay stress on the great difference between the anesthetic action and the more subtle toxic action, which may be produced from concentrations too small to cause anesthesia and, therefore, insufficient to give warning of danger. The personal equation plays a large part in cases of intoxication by this group of solvents. It is not rare to have a large number of workers using carbon tetrachloride or trichlorethylene with no apparent discomfort, and suddenly one of them develop symptoms of intoxication without any increase of exposure. Pagniez[246] reported 3 cases, all exposed to the same fumes of CCl_4 for the same length of time, one of them mild, one severe, one fatal.

Carbon tetrachloride or *tetrachlormethane* (CCl_4) is industrially the most important member of this class. It is familiar to the public as a chemical fire extinguisher and as a non-inflammable dry cleanser, to the medical world as an anthelmintic. A great deal of experimental work has been done on this compound both in connection with its therapeutic use and its use in industry, but the cases of intoxication have come chiefly from its industrial use. It is a narcotic with an action very like that of chloroform though not so strong. On the other hand the after-effects of severe narcosis seem to be more serious than are those of delayed chloroform poisoning, and they occur more often.

Industrial poisoning from CCl_4 is typically acute with symptoms of narcotic intoxication, followed by symptoms pointing to liver and kidney damage, which appear after an interval of about 6 to 24 hours. In the early days of anthelmintic therapy there were a number of accidents because certain persons proved to be very susceptible to the action of CCl_4. These were chronic alcoholics, people with damaged hearts and kidneys and those with malnutrition especially from a low calcium diet. Animal experiments showed that the attack is especially on the intestinal tract and the liver, much less on the kidneys, that a negative calcium balance increases the susceptibility and that alcohol increases its action, as does also a fatty diet just before the dose (Lamson and associates[176,177,178]). In man, when CCl_4 is given by mouth, much the same results are produced, but in industrial cases, which follow inhalation, the symptoms of renal damage overshadow those of hepatic injury. The history is usually the following; nausea, vomiting, abdominal pains, diarrhea, headache, dizziness, then dark colored urine, which often is the first thing that sends the man to his doctor, and later on jaundice, then increasing oliguria with the urine loaded with casts and albumen. Complete anuria may last for some days, 10 in Dudley's case[58], and then clear up, or it may persist until death with symptoms of uremic poisoning. Three cases of nephrosis from CCl_4 poisoning, 2 of them fatal, were reported in 1939 by Smetana with an excellent review of the whole subject[293].

The latest instance of acute nephrosis is that reported by Corcoran and his colleagues[43] in a welder, who used carbon tetrachloride to prevent explosion when he welded a tank that had held gasoline. These authors find that the form of nephrosis is that caused by toxic agents; that it is essentially a process destructive of the epithelium of the kidney, the stroma being left intact so that complete recovery may occur through epithelial regeneration.

The literature of CCl_4 poisoning contains some unusual clinical pictures. One of Dudley's[58] patients had an exposure of only 5 minutes to heavy fumes from a fire extinguisher, but 9 days later he developed epileptiform convulsions, a blood pressure of 220/90 and an acute uremia of severe character. He finally recovered.

A fatal case after only $2\frac{1}{2}$ hours' exposure in a large, well-ventilated machine room occurred in Germany in 1941. Death was due to pneumonia, which followed symptoms of poisoning involving the digestive tract, liver and kidneys.

A case, not of industrial origin but caused by the use of a " pyrene " fire extinguisher in the interior of an automobile, was described by Hagen and his colleagues[110]. The man inhaled the fumes for about half an hour with no immediate symptoms of any severity. He took a couple of drinks of alcohol and had a good night but the next morning began to suffer from nausea, vomiting, malaise, diarrhea and numbness of hands and feet. Later, grave hepatic and renal damage appeared

with hemolysis and some pulmonary damage. There were also nervous symptoms, hiccough, mild convulsive seizures, increased muscle tonus and hyperactive reflexes. Recovery came after some 3 weeks in hospital.

Wirtschafter[343] was the first to describe visual changes following intoxication of a fairly minor character. Five men, dry-cleaners, who complained of headache, dizziness, nausea, vomiting, etc., showed bilateral peripheral constriction of the color fields but no central scotomata. Two of them had not noticed any change in their vision; the other 3 complained of spots before the eyes, blurring, and " everything looked small ". Wirtschafter, acting on Lamson's experimental finding that a fall in blood sugar occurs in animals treated with CCl_4, made blood sugar tolerance analyses and found the amount in all 5 men to be at the lower border of the normal variation and sometimes below this. There were small amounts of sugar in the urine after fasting, which increased after the giving of glucose, and both the blood and the urine returned to normal, when the men left work and were put on Minot's diet of calcium and dextrose[220]. He suggests that a routine examination of the peripheral visual field may be useful in revealing intoxication at a very early stage. H. F. Smyth[298] agrees with this. Among 93 men whom he examined he found 10 with the visual field restricted as much as 30 per cent. toward the bottom and outer edge and 16 with less certain evidence.

Other atypical and dubious forms are those, which are predominantly nervous in character. André Domart in a Paris thesis written in 1938 describes cases of polyneuritis following a hepatorenal type of poisoning. A case of progressive spinal muscular atrophy is attributed by Kinney[162] to carbon tetrachloride poisoning. Hagen's[109] patient had a series of severe epileptiform attacks, coma and convulsions, which began on the eighth day following acute intoxication while cleaning a filter with CCl_4.

Chronic poisoning, developed gradually in the course of prolonged exposure to small quantities of CCl_4, is much rarer and less characteristic. Butch[30] had a case, which belongs in this class, one with symptoms simulating portal cirrhosis, a condition which Bollman and Mann had produced in dogs. Poindexter and Greene[259] found at autopsy on a workman, who had experienced long exposure to carbon-tetrachloride, cirrhosis of the liver with ascites and infarction of the right kidney and compensatory hypertrophy of the left.

For a long time fairly high concentrations of carbon tetrachloride, even up to 1,000 parts per million or higher, were considered as allowable in industrial establishments. However, more than 10 years ago P. A. Davis[49], who has had a long and extensive experience with the use of this solvent by the Goodyear Rubber Company, decided that anything over 100 parts per million is dangerous for continued exposure, and that figure has been approved tentatively by several state codes as the maximum allowable concentration. Even though this standard is

adhered to, Davis advises a careful selection of workers with rejection of the obese and the undernourished, nephritics, diabetics, those with lung or liver pathology and those having an enlarged thymus or thyroid. He warns of the possibility that free chlorine or hydrochloric acid may be present in commercial CCl_4 and cause bronchitis or bronchopneumonia. Elkins[66] of Bowditch's staff in Massachusetts and Heimann and Ford[133] of Greenburg's in New York have found mild symptoms of narcosis in workers where the concentration of CCl_4 was lower than 100 parts per million. Elkins thinks that this level is too high, that the limit should not be over 50 parts per million.

Carbon tetrachloride, in spite of its unpleasant odor, has in some men a pleasantly intoxicating effect, and cases of addition have occurred in Germany and in this country.

E. F. Russell[270] believes that women are more susceptible to carbon tetrachloride than men, that cigarette smoking increases their susceptibility, and that one result is abnormally frequent menstruation.

Trichlorethylene. — Next in importance industrially comes trichlorethylene, which can serve the same purpose as CCl_4 in many cases, and often is preferred to the latter as less toxic. For some years after its introduction it was recommended as an ideal non-inflammable and non-poisonous degreaser and lacquer thinner, but evidence from England and Germany soon proved that it is a strong narcotic and even pointed to serious systemic damage. In England 38 cases of severe acute poisoning with 3 deaths from the industrial use of trichlorethylene had been reported to the Home Office by 1935. From Denmark came 5 cases. Much the most important publication in this field came from Germany, the monograph by Katharina Stüber[304], which appeared in 1931 and recorded 284 cases with 25 deaths. Von Oettingen[240] collected from the literature 7 additional fatalities between 1931 (Stüber's date) and 1937 and 8 non-fatal cases. Pies[256] in 1939 added 2 more cases to the German list of victims of trichlorethylene poisoning, both in women who fell unconscious while at work. One recovered fairly soon, but the other was unconscious and cyanotic for some time and developed bronchiolitis and bronchopneumonia with fever.

The most striking characteristic of trichlorethylene is its acute narcotic action. Lehmann[184] says it is to chloroform as 1.7 to 1.0. By far the larger number of cases in man are acute in character. In Stüber's list of 19 fatal cases, whose history was known, 12 were acutely narcotized and died without regaining consciousness. Three fatal cases in the German factory inspectors' reports of 1935 belong in this class. Of the 39 English cases all but 2 were severely narcotized; 3 died; the others recovered completely. That recovery without lasting injury is to be expected is shown in the study made by Striker and his colleagues[303] of the histories of 304 patients on whom " tri " was used as an anesthetic.

Stüber's list contains cases not only of acute narcotic intoxication but of chronic poisoning with marked damage to the central nervous system especially but also to the vascular system and to the liver, spleen, lungs and kidneys. Her report aroused much interest and started a controversy that still goes on. While it is certainly true that organic injury is seen rarely in cases of industrial trichlorethylene poisoning, some cases have been reported.

Practical experience with this solvent shows that it causes more discomfort, more minor complaints among workers, especially women, than does " tetra ", because of its strong narcotic action. In hot, humid weather especially there will be many cases of headache, dizziness, confusion and fainting, but the severe symptoms pointing to organic damage, which sometimes follow acute CCl_4 poisoning, appear only rarely. Willcox[335] saw a case of toxic jaundice following exposure to trichlorethylene, and Browning describes one of jaundice with enlarged liver occurring in a lad after six months' exposure to " tri " [24].

Reports of severe damage to the central nervous system come from Germany; Kunz and Isenschmidt[174] describe a case of polyneuritis of all four limbs, paralysis of the hypoglossal nerve and retrobulbar neuritis in a man of 56 who had worked with trichlorethylene for a year, while Persson's[254] 2 patients, degreasers, developed symptoms of spinal cord injury, spastic ataxia, strongly positive Romberg and disturbed sensation in feet, hands and forearms. In Stüber's report 182 out of 284 cases are listed as chronic, and the symptoms cover a wide range; functional neuroses, paralysis of cranial nerves, epileptoid seizures with psychic disturbances, anemia, gastrointestinal disorders. On the other hand, according to Browning[23], John Bridge, the Chief Medical Officer of Factories and Workshops, finds little proof of chronic poisoning. Only one case of the 30 reported seems to belong in that class, a woman, who for some weeks complained of pain in the chest, dyspnea, anorexia and loss of weight. She was slightly anemic. Three persons, who had been exposed for a year or more under poor conditions, were examined carefully by Bridge for evidence of organic damage, but none was found, although all 3 complained of subjective symptoms attributable to a narcotic poison.

Animal experiments tend to confirm clinical evidence that organic lesions are rare, although McCord[208] found in his experiments very severe lesions in all important structures. However, the great majority of workers find no characteristic changes in liver or kidneys. Barrett and his colleagues[11] compared the toxicity of trichlorethylene and carbon tetrachloride, a point of great practical importance, since one can be substituted for the other in many industrial processes. They found that guinea pigs were very susceptible to organic damage from CCl_4. Exposure to 1200 p.p.m. resulted in hemorrhage and in degenerative changes in the liver and kidneys. The same exposure to " tri " for more than 1,100 hours caused

no pathological change in any organ except the liver, and even there it was so slight as to be probably of no significance. They agree with Lehmann, however, that trichlorethylene is the more powerful narcotic of the two.

Hammes[122] gives the history of an acute, severe intoxication developing suddenly after one day's work with CCl_4, in a man who had used trichlorethylene on the same job for 3 years without any trouble. In this case there was only slight involvement of the liver but marked involvement of the kidneys.

An unusually severe case of trichlorethylene poisoning was seen by one of us (R.T.J.). A man was put to cleaning machine parts in a large tank of " tri " in a far corner of the plant where ventilation was poor. He soon complained of dizziness, and after two hours and a half he fell to the floor unconscious, arriving at the hospital comatose. Profuse sweating was noted. He had deep respirations, slow but increasing in frequency, a pulse of 86 with blood pressure 102/70. As soon as the cause was learned, oxygen was administered, and he recovered consciousness in half an hour but vomited repeatedly for several hours complaining of severe pain in the head and the abdomen. Recovery was complete. Ethel Browning[24] reports 2 cases of severe anemia, which she tentatively ascribes to trichlorethylene, one aplastic in form and fatal, the other, hypoplastic.

An important and still unsettled point is the specific action of " tri " on the sensory branch of the trigeminal nerve, which Plessner[258] described in 1916, and which gained such general credence that trichlorethylene, under the name of chlorylen, was widely used to stop the pain of facial neuralgia. Much scepticism has, however, developed of late concerning this theory. Plessner's cases, 4 men with complete sensory but not motor paralysis of the fifth nerve, occurred during World War I, when German factories were obliged to use all sorts of ersatz material and in a factory where no such form of sickness had ever occurred before. All 4 sickened at the same time. Some 12 years later Kalinowsky[158] saw 2 men with practically identical symptoms, but they had been exposed not to trichlorethylene but to a mixture containing some unidentified chlorinated hydrocarbons. In Stüber's 10 cases of trigeminal paralysis, all industrial, there is no proof that " tri " was the only compound present. Moreover, the therapeutic use of pure " tri " seems to show that its effect is not paralyzing but only narcotic. Eichert[65] reviewed the literature covering this form of treatment of trigeminal neuralgia and could find no evidence that the prolonged use of this drug was followed by injury to the fifth nerve, even in cases of addiction.

Eichert makes the same statement with regard to optic nerve injury, which also has been described as characteristic of poisoning from trichlorethylene. In Stüber's collection there are 9 cases of visual disturbance, ranging from alteration of the color sense to optic nerve atrophy. Baader (see Stüber) saw 2 cases following long exposure. Retrobulbar neuritis following 14 months' exposure occurred

in a case that was reported to one of us (A.H.) a few years ago, but in none of these can we be sure that trichlorethylene alone was the active agent. The same doubt arises as to the 2 cases of angina pectoris reported by Gerbis[88] and to the cases of cerebral hemorrhage (Plessner, Stüber, Kalinowsky.) Stüber assumes as the cause of these cases a vascular injury such as sometimes follows acute carbon monoxide intoxication and results in thrombosis or hemorrhage.

Koch[165] made an autopsy on the body of a workman, who died from breathing fumes from a hot degreasing kettle in a basement, and he found extensive lesions in the respiratory tract beginning in the lower third of the trachea, where the epithelial lining was completely desquamated. The alveoli were filled with blood cells and fatty epithelial cells. Hansen's[123] case had a similar origin, but here there was an extensive tuberculosis. In Christiansen's[41] case, which he regards as a confirmation of Koch's, there was a widespread pathological process in the lungs resembling in the x-ray picture a miliary tuberculosis. This man recovered after 5 months. In all of these cases one must remember the possible presence of Cl, HCl, $COCl_2$ and, according to von Oettingen[240], of dichlorethane in the fumes.

Trichlorethylene according to Barrett and associates[11] is more likely to give rise to addiction than is carbon tetrachloride because the fumes are less nauseating. The maximum allowable concentration has been placed tentatively at 200 parts per million, because the margin of safety is distinctly wider than is that for CCl_4.

Recently an interesting contribution to the action of trichlorethylene has come from a non-industrial source. A. M. Geiger[87] describes a case of intoxication from the therapeutic use of " tri ", which was characterized by profound loss of consciousness and " multiple focal ventricular tachycardia of an ominous type, likely to lead to fatal ventricular fibrillation ". This condition appeared repeatedly under therapeutic inhalations, first of pure " tri ", then of pure carbon tetrachloride. Geiger suggests that here may be found an explanation for mysterious sudden death occurring from the industrial use of " tri ". Confirmation of his findings is afforded in a recent publication by Waters, Orth and Gillespie[324], calling attention to cardiac arrhythmias noted by them in 10 patients and 7 dogs during anesthesia with trichlorethylene. Multiple focal ventricular extrasystoles and ventricular paroxysmal tachycardia were seen several times among 6 patients followed with electrocardiograms.

Tetrachlorethylene is, according to Lamson, Robbins and Ward[178], much safer than is CCl_4 when given by mouth. In their animal tests they found it was absorbed from the gastrointestinal tract only if a large amount of fatty food had been eaten just before. Autopsy on animals, which had reecived it by inhalation, showed no fatty degeneration in the organs. These authors believed it to be the

safest member of this group for therapeutic use. The experiences of Fernando and his colleagues in India is in harmony with Lamson's findings. They tested the toxicity of tetrachlorethylene on 111 patients, finding " no appreciable toxic effect on the liver in any of them, even in those receiving double the maximum adult dose in general use ". There was no depressant action of any importance and no toxic action on the kidneys.

Tetrachlorethylene is now in fairly extensive use in industry, but so far no reports of the effect on workers, who are exposed to the fumes, has been published.

Ethylene dichloride, sometimes called ethylene chloride but which really is dichlorethane, has come into prominence recently as an excellent solvent and a dangerous poison. It is used in the separation of wax from petroleum, in oil extraction, in dry cleaning, in the production of photographic films and as a thinner in lacquers, especially for coating the interior of beer vats. The last was the source of 2 severe cases reported to one of us (A.H.) by State inspectors. In 1937 von Oettingen[240] could find no industrial case reported in the literature, but two years later Wirtschafter and Schwarz[344] saw 3 cases in men, who used this solvent for cleaning yarn, working over an open vat in a hot room (75° F.), lifting out the yarn and wringing it by hand. The effect was characteristic of a narcotic poison, but, in addition, there were severe dermatitis of the hands, leukocytosis of 12,400 to 18,250 and liver disturbance, as shown by extremely low blood sugar levels, but no evidence of kidney involvement. Recovery followed removal from the fumes and treatment with calcium and a high carbohydrate diet. They conclude that it is less toxic than CCl_4.

Sayers and his colleagues[272] tested ethylene dichloride on animals and found that inhalation of air containing 1 per cent. for 20 minutes caused the animals, after a day or two, to die with congestion and edema of the lungs and secondary degenerative changes in the kidneys. The narcotic action is about equal to that of $CHCl_3$ and CCl_4, but there are less serious sequelae.

McNally and Fostnedt[214] report 2 cases of chronic poisoning in men who had been exposed, one for 2 months and the other for 5 months, to the vapors of ethylene dichloride (dichlorethane). The symptoms consisted in anorexia, nausea, vomiting, epigastric distress, drowsiness, tremors and nystagmus.

Tetrachlorethane is, by common consent, the most toxic of the chlorinated hydrocarbons that have been used in industry. Penta may be more so, but we know little about it. It came into prominence during World War I, when the wings of war planes were covered with a dope of cellulose acetate, and tetrachlorethane is its best solvent. The Germans had discovered its dangerous nature before the war broke out, for there had been in airplane plants a number of cases of acute yellow atrophy of the liver, and the pharmacologists, Grimm, Heffter and Joachimoglu[104], had identified this constituent as the one responsible, but none

of that information reached England, and the English had to go through the same experience, toxic jaundice in airplane dopers, the cause to be discovered by Willcox[333], and a resultant discontinuance of its use. We were warned in time by the English and escaped that particular danger. The first reported case in American industry came from the manufacture of acetate rayon, but the solvent is used no longer in that industry.

For many years we heard nothing about this solvent beyond occasional rumors that it was being used in coatings, in laundry " mix " and in non-inflammable film production, but no cases of poisoning were reported. Now, however, we are told that it is coming back into use, a fact to be deplored, if true, for it is highly toxic, although fortunately its volatility is low; it is six times as heavy as air.

Characteristically tetrachlorethane is absorbed slowly and its action is prolonged. One does not read reports of acute narcosis but rather of vague symptoms, nervous and digestive, which slowly progress to serious illness. The form most often described is acute yellow atrophy of the liver, which appears in British factory inspection reports under the head of toxic jaundice, along with arsine poisoning. The immediate cause of death in both these classes may be hemorrhage from stomach or intestines or from the nose. Finally, the Germans report cases with a predominance of nervous symptoms and no apparent injury to the liver (Brezina and Teleky[22]).

Minot and Smith[223] were able to detect in men and women exposed to mild concentrations a characteristic change in the leucocytes which may serve as a warning that absorption and damage are taking place. This is the appearance of a relatively large number of leucocytes of the endothelial type, which may run as high as 40 per cent., the cells showing degenerative changes more and more as their number increases.

Penta- and *hexa-chlorethane* are coming into industrial use. Hexa is said to be a constituent of a secret explosive. Theoretically they should behave much as does tetrachlorethane, but we have as yet no data concerning them.

Methyl chloride or *monochlormethane* is used very extensively as a refrigerant, and most of the instances of intoxication, whose histories have been published, have been caused by the escape of fumes into dwellings; only a minority were of industrial origin, in makers or repairers of refrigerators. Most of the cases of industrial intoxication, which have come to light, are the result not of acute narcosis but of repeated exposures to small doses, which gradually cause injury to the central nervous system. The earliest industrial cases were characterized by increasing fatigue, lassitude, anorexia, muscular weakness and finally, somnolence and dimness of vision. To this picture nausea, vomiting, restlessness and insomnia sometimes were added, also ptosis, fine tremors and staggering gait. Baker[9a] found formic acid in the urine. No fatality from the industrial use of methyl-

chloride has been reported, unless one accepts a case, described by Schwarz[279], in a man who was very nervous for three weeks after an acute poisoning, and then lost consciousness and died in convulsions. From the animal experiments of Sayers and his colleagues[273] and from the autopsies on the victims of the mass poisoning in Chicago in 1929 (Kegel and associates[159]) it is evident that methylchloride causes an acute nephritis with degenerative changes in liver and spleen, hemorrhages in lungs, intestinal tract and dura, and, in the Chicago cases, primary anemia with leucocytosis. Of those that survived in that epidemic a number had some sequelae, usually of a character to indicate degenerative changes in the central nervous system.

The most recent case in the literature comes from England. In 1940 Chalmers and associates[38] examined a refrigerating engineer, who was acutely intoxicated by methylchloride, with delirium, convulsions and tremors. They found large quantities of coproporphyrin, series III, in urine and feces, disappearing with the disappearance of the toxic symptoms. Recovery was not complete till the end of the seventh week.

A. M. Jones[157] reports 7 English cases, but only one was severe, the first one of that character to be reported in that country. The men were refrigerator repairers and, since the gas is not disagreeable, all had inhaled it in the course of their work in sufficient quantity to cause headache, dizziness, staggering gait, followed some hours later by nausea and vomiting. Loss of appetite was common. However, the men were not incapacitated, and the only observed sequelae were attacks of depression and vomiting. Eye symptoms were common, misty vision and diplopia. In the severe case there was involvement of the central nervous system and hepatic and renal damage and depression of marrow activity.

There has been a great increase in the use of methyl chloride for refrigeration since the present war began and for air conditioning in the place of freon, dichlorodifluoromethane, which now is largely preëmpted for use as a disperser of insecticides. Engineers warn that methyl chloride is inflammable and explosive as well as toxic.

Ethylene chlorhydrin is reported to have caused 2 deaths in German industry (Koelsch[169]) and 2 severe cases, one fatal, in English (Middleton[219]). It is a by-product in the making of synthetic indigo and is a good solvent for fats. The action is that of a narcotic poison with characteristic lesions in liver, spleen and lungs.

Chlorinated naphthalenes. — These very valuable insulating waxes are compounds of naphthalene with a chlorine content which runs from about 20 to 65 per cent. The products of higher chlorination came into use later than the lower ones. In this country they are known as halowax, and this wax has been a notorious source of acne, " cable rash " or " blackhead itch " often of a severe type

(Mayers and Silverberg[205], Sulzberger, Rosenberg and Scher[305] and Schwarz[282]). The Germans described it under the name of " chloracne " caused by " perna ", a mixture of these compounds[310].

For some twenty years halowax was used in electrical insulation without any more serious injury to the users than skin lesions, but when the higher members of the group, penta and hexa, came into use, cases of fatal jaundice, acute yellow atrophy of the liver, began to appear, few and scattered, but fortunately in States where such cases are investigated carefully. In 1936 3 fatal cases were recognized as linked up with exposure to fumes of halowax, either melted or dissolved in carbon tetrachloride and ethylene dichloride. The industrial hygiene bureaus of New York, Connecticut and Massachusetts were unable to get any history of similar cases among users of chlornaphthalenes in foreign countries. But in 1938 the Annual Report of the Chief Inspector of Factories for Great Britain made a brief statement about 3 fatal cases of toxic jaundice which were traced to inhalation of fumes of chlornaphthalene.

The 3 original cases are summarized in a paper by Flinn and Jarvik[77], who also succeeded in producing fatal liver lesions in animals by injections of chlornaphthalenes from tri up to hexa. The histories of these cases are given in full by Greenburg and associates in The Industrial Bulletin, State of New York, *18*, No. 40, 1939. At this time the purveyors of halowax, the Halowax Corporation, asked C. K. Drinker and his colleagues[55] of the Harvard School of Public Health to make a thorough study of the problem. These investigators succeeded in producing severe lesions in the liver by means of penta- and hexa-chlornaphthalene, the more readily when the action of CCl_4 was added to that of the chlornaphthalenes. With tri and tetra the lesions were much less serious. Drinker adds to the first 3 human cases 4 non-fatal ones. It is interesting to note that in their animal experiments he and his colleagues found that rats, which had shown no clinical evidence of disease from the chlornaphthalenes, would die promptly, if they were given a small dose of CCl_4. Lesions always were confined to the liver. In 1942 Mayers and Smith[206] reported the history of a non-fatal case of toxic jaundice in an 18-year-old girl, who had breathed fumes of chlornaphthalenes, which were given off when she used a soldering iron on condensers impregnated with chlornaphthalene wax. The first symptom noted in this case was edema, which appeared before the icteroid tinges in the sclera. Later there was jaundice with anorexia, nausea and severe abdominal pains, but edema was the outstanding feature. The authors hold that the edema was produced by hypoproteinemia caused by the liver damage (serum albumin 1.7 gm. per 100 c.c., serum globulin 2.5 gm. per cent.) and that it can be controlled by increasing the blood protein.

Up to 1942 the only published histories of this form of poisoning were all of American origin, but in that year the first English case was described in detail

by McLetchie and Robertson[212], a case of toxic jaundice in a woman who for six months was exposed to chlornaphthalenes. Some of her fellow workers had the usual acneiform eruptions, but there was no other case of jaundice. The illness came on slowly, jaundice appeared and increased, the patient passed into coma and died in the fifth week.

Just recently Greenburg[99] has reported an outbreak of toxic jaundice in two factories in New York State producing insulated wire and other electrical apparatus. In one of them 2 fatal cases of acute liver disease occurred in the spring of 1942; in the other there were at least 4 fatal cases during the year and several of systemic poisoning requiring hospital care as well as many cases of acne.

Drinker's studies[55] show that the allowable concentration for the lower members of the group, such as trichlornaphthalene, is 10 mgm. per cubic meter of air, but for the higher members, such as penta and hexa, it should not go over 0.5 mgm. They also warn against the use of carbon tetrachloride as a solvent, for that greatly increases the danger. Preventive measures should be based on the fact that the vapors are much heavier than is air. The examining physician should be careful to reject men, who might already have liver damage, e.g., syphilitics under arsphenamine treatment. Greenburg warns against allowing a worker, who shows any evidence of even mild liver damage, to go back to work, for the result may be fatal.

Another source of " chloracne " has come to light lately, *cutting oils to which organic chlorine compounds have been added.* The mists from such oils used in heavy cutting and grinding operations cause skin lesions like those of " cable itch ".

Bromine Compounds of the Hydrocarbons

These are less narcotic but much more toxic than the chlor compounds. Fortunately they are far less useful in industry. Methyl bromide, ethyl bromide and ethylene dibromide have been used as refrigerants, especially abroad. Sayers and Yant[273] tested these compounds on animals and found methyl bromide much the most toxic. The known cases of poisoning by bromine derivatives, usually methyl bromide, come to us from foreign reports, German and Swiss chiefly. Even in those countries they are rarities.

Methyl bromide has come into extensive use in this country as a fumigant for foods, to get rid of insects. It is shipped as a liquid in cylinders and either allowed to evaporate directly into the fumigation area or conveyed there by pipes. Although it has been used thus for some years and on a large scale, no reports have reached us of harmful results. One of the very rare cases of industrial methyl bromide poisoning in this country was reported to one of us (A.H.) in 1926. This was in a man, who inhaled the gas while charging a refrigerator, made no com-

plaint at the time, was seen to stagger home two hours later and fell unconscious at his door. He had a series of convulsions suggesting uremia, and catheterization showed the bladder to be empty. He died nine hours after his exposure. Methyl bromide poisoning has several unique characteristics; a definite latent period, a profound action on the motor system with violent jerkings or clonic convulsions, visual disturbance from retinal hemorrhage, fever, delirium, coma and after death, a complete disappearance of the poison from the tissues and fluids of the body (Irish and associates[150]). Victims who survive show evidences of profound injury to the nervous system.

Recently Watrous[425] has published his observations on 90 men exposed to low concentrations of methyl bromide, less than 35 parts per million. He found symptoms of mild intoxication in 33, skin lesions in 22. Watrous warns that organic matter such as rubber and adhesive tape may retain methyl bromide a long time. The action of ethyl bromide is chiefly on the kidney, and a diffuse acute parenchymatous nephritis is the most prominent change found in animals dying from exposure to the fumes. For ethylene dibromide see Thomas and Yant[315].

Aromatic or Benzene Series of Solvents

Coal Tar Benzene or Benzol

Coal tar benzene or benzol is the most dangerous of the industrial solvents with the exception of tetrachlorethane. It is so recognized in industry, and its use has been abandoned, often at a good deal of sacrifice, by conscientious employers, who refuse to subject their workers to such a risk. Many, however, have been obliged to go back to its use now, since toluene cannot be secured because it is needed for trinitrotoluene.

Benzene was brought to the attention of the medical world first in 1897, when Santesson[271], a Swedish toxicologist, read a paper before the International Medical Congress in Moscow, in which he described 9 cases of hemorrhage under the skin and from mucous membranes in girls using benzene rubber cement in a tire factory, 4 of these cases ending in death. Then 13 years later Selling[286] of Johns Hopkins reported 3 similar cases in girls using a benzol rubber seal for tin cans. Selling made many experiments on animals and established the basic facts underlying the pathology of benzene poisoning, namely, that it acts chiefly on the blood forming tissues, the marrow of the long bones and the lymphatic structures, producing anemia and granulocytopenia together with a loss of the clot forming substances in the blood.

The clinical picture that emerges from these early studies is one of progressive weakness, dizziness, headache and vomiting, then the appearance of purpuric spots on the skin, bleeding from gums, throat, nose and uterus and in fatal cases,

death from severe hemorrhage or toxemia.

Selling's work in the experimental field was confirmed by many students, who found that in animals the most important effect is leucopenia; the fall in the red cell count is far less striking; the most important change found postmortem is aplasia of the bone marrow; damage to the lymphadenoid tissues is far less important. Among the leucocytes the polynuclears suffer the most. In the early stage of poisoning stimulation of cell production is seen in the marrow accompanying the destructive process. Regeneration can occur after an advanced degree of aplasia. Benzene also is a direct leucotoxic poison acting on the white cells of the circulating blood.

Other features were added to Selling's findings. Duke[60] found in rabbits a rapid rise in the platelet count followed by a rapid fall, while the bone marrow showed almost complete absence of megacaryocytes. Animal experiments also showed the effect of benzene on the formation of antigen. Rusk[269] found a reduction in the formation of lysin for sheep's blood and of precipitin; Simonds and Jones[292], a loss of hemolytic and agglutinating substances; Hektoen[135], a loss of lysin and precipitin; Winternitz and Hirschfelder[342], reduced resistance to pneumococci; White and Gammon[328], to tubercle bacilli. Camp and Baumgartner[31] found that benzolized animals failed to have a normal reaction to injuries produced by heat, chemical irritants and unsterilized foreign bodies, i.e., no leucocytosis and no increase of leucocytes in the injured area.

Those years produced more careful experimental work with benzene than clinical studies, and because of this a standard for diagnosis emerged which was based on animal response, not on human.

It is a serious error to assume that all the observations made on animals are true of human beings with benzene poisoning, for there are marked differences. Thus Hurwitz and Drinker[147] found only slight signs of hemorrhage in their experimental rabbits and, as a rule, no prolonged bleeding time. Even more important is the difference in the degree of anemia. In animals leucopenia is far more striking than anemia, and it was assumed for many years that that was true also of benzene poisoning in working people; therefore that the earliest and most trustworthy sign was a fall in the white cell count, below 5,000, a red cell count being unnecessary. Many early cases must have been missed under this mistaken procedure, for in man the loss of red cells may be greater than the loss of white cells and it may appear earlier.

Acute benzene poisoning is of little importance under modern industrial management. The danger is well understood, and no longer are men sent unprotected into tank cars or vats. It is a narcotic poison, which acts with great swiftness producing unconsciousness or helpless confusion. In such cases it is often the rescuer, exerting himself to save the victim, who gets a fatal dose, while the

passive victim survives. As a usual thing recovery in non-fatal cases is complete with no sequelae.

Chronic poisoning is far more important. It comes on slowly, the symptoms are vague, and often it is not till the stage of hemorrhage has been reached that the victim seeks help. The bleeding may be from the nose, the gums, the uterus, into the subcutaneous tissue, more rarely into the retina or stomach or intestines. An examination of the blood at this stage shows marked changes, an anemia of the non-regenerative type, a granulocytopenia, prolonged bleeding time and delayed clotting. In such cases the diagnosis is easy, if benzene exposure has taken place. The process may be halted under appropriate treatment, or it may progress even to a fatal ending without any further exposure. This fact is stressed by Selling and Osgood and a number of such instances are to be found in the literature (Rohner and Baldridge[266], Andersen[2]).

For the physician the most important task is to detect benzene poisoning in the early stage before serious damage has been done. Blood and urine examinations should serve to reveal this stage.

Theoretically there should be a stage of marrow stimulation with high blood cell counts and immature forms, and actually this stage has been observed. Teleky and Weiner[311] found in the blood of women benzene workers nucleated red cells, anisocytosis and poikilocytosis. Ross-Smith[294] found a high red cell count, over 5 million, in 14 out of 71 women, also an increase in large epithelioid cells.

As for the diagnosis of benzene poisoning in the very early stage opinion has changed very decidedly in recent years. As the study of benzene poisoning in man has proceeded, the simple picture formerly established has had to be abandoned and the fact accepted that benzene is a bone marrow poison, whose action may be exerted now on one element of the marrow, now on another. There may be polycythemia or anemia, leucocytosis (polynuclear or lymphatic) or leucopenia, there may be a complete absence of youthful forms or abnormal forms, there may be reticulocytes, myelocytes, anisocytosis and poikilocytosis, eosinophilia, megalocytosis. The color index may be low, normal or high. Benzene is a bone marrow poison, but the attack may be now on one element, now on another; indeed there is evidence to show that a stimulation of one may go on at the same time as destruction of other elements[118,278].

Donald Hunter[145] saw an illustrative case in a young girl, who was exposed for 4 years to fumes from a mixture of 7 per cent. benzene with Russian benzine, which contains a fairly high percentage of benzene. On her first examination she was clinically well except for purpura of the limbs and a past history of menorrhagia. The first blood count showed a reduction only of platelets, 51,000, and of polynuclear leucocytes, 40 per cent., but the red count was 5,100,000, the white, 7,600. However, only 48 hours later she had severe bleeding from the gums,

lungs and gastrointestinal tract. The platelets disappeared from the circulating blood, the red cells fell to 1,000,000, but the white cells rose to 15,000. Under a mistaken diagnosis splenectomy was performed, and the peritoneal cavity was found full of blood. She survived the operation and slowly recovered, the platelets reappeared, 132,000, in the second week, the red cell count rose to 3,300,000, white cells were 8,200 with polynuclears 41.5 per cent. Another English report by Hamilton-Paterson[121] in 1941 confirms these findings. The author describes 3 cases of poisoning, one fatal, and also the blood changes in 18 other women exposed to benzene. The blood picture varied greatly, anemia, polycythemia, leucopenia, leucocytosis, relative decrease, relative increase of polymorphonuclears and eosinophiles.

Andersen's[2] case is a contribution to the literature of atypical benzene poisoning. Here there were several interesting features. The disease developed about 5 months after exposure, and continued to progress for 18 months after exposure had ceased; death was caused by general septicemia, streptococcus hemolyticus; the red blood cells showed marked variations in size and shape with polychromatophilia and basophilic stippling. Two normoblasts were seen. The polymorphonuclear cells were young, showing a marked shift to the left. A few weeks before death the reticulocytes made up 12.3 per cent., normoblasts 10 per cent., and there were monocytes, myelocytes and myeloblasts. Autopsy revealed hyperplasia of the marrow and acute splenic tumor.

A recently discovered aid in the diagnosis of early benzene poisoning is the urinary test devised by Schrenk, Yant and Sayers[276] of the Bureau of Mines. They found uniformly in a series of about 100 animals an early sign of benzene poisoning in the urine, namely, a decrease in the proportion of inorganic sulphates to total sulphates, this decrease being marked in accordance with the severity of the intoxication. The same decrease was found in benzene workers.

Normally the inorganic sulphates make up 85 to 95 per cent., the organic, ethereal or conjugated, 5 to 15 per cent., but in cases of benzene absorption the phenolic products that are formed take up the sulphur, and the result is an increase in the conjugated sulphates which reverses the above proportions. "The most important fact relating to this test is that the decrease occurs rapidly on exposure to benzol and well in advance of leucopenia or anemia or other evidence of damage "[276].

In other hands this test has proved of minor value. The studies made by the Boston and New York groups[18] showed that it failed in some cases of clinical poisoning and could not be depended on to reveal absorption of benzene. Like conclusions were made by the Public Health Service.

Vigliani[251], who has seen many cases of benzene poisoning in Italian rubber works, divides them into four classes: (1) those clinically, hematologically and

anatomopathologically typical of aplastic anemia; (2) those clinically typical of aplastic anemia but showing an active hemopoiesis especially in the bone marrow, pseudo-aplastic anemia; (3) those with a typical aplastic anemia with myelitic hyperplasia or metaplasia resembling leucemia especially in liver and spleen; (4) those with chronic or acute leucemia, not infrequently appearing as aleucemia. All these forms have been demonstrated experimentally in animals.

As to the fourth class, evidence is piling up that leucemia, myeloid or lymphatic, may be one of the forms benzene poisoning may take. Vigliani and Penati collected 10 cases, which had been reported by 1938, and Mallory and his colleagues have added 2.

It may be well to give a brief summary of the newer additions to our knowledge of this form of industrial poisoning, which we owe to the studies made by a group in New York (Division of Industrial Hygiene, State Department of Labor and Hospital of the Rockefeller Institute) and a group in Boston (Division of Occupational Hygiene, State Department of Labor and Massachusetts General Hospital[18]).

(1) The diagnosis of benzene poisoning, mild or severe, must be made on the whole blood picture, and the earliest and most frequent deviation from the normal consists in a fall in the red cell count and an increase in the mean corpuscular volume of the red cells. A fall in platelet count and a reduction of hemoglobin follow in frequency, but a fall in the white cell count is less characteristic of early poisoning than any of the above. Anemia and macrocytosis are the changes to be looked for.

(2) Increase of urobilinogen and deviation from the normal urine sulphate partitions were not found to be of value in diagnosis.

(3) Bleeding time and coagulation time were of no aid, being prolonged only in severe cases.

(4) Clinical symptoms, weakness, fatigue, epistaxis, dryness of the throat, anorexia, nausea, dizziness, insomnia, were of dubious value, because, although they were present in workers exposed to benzene more than in controls, they were absent in some cases of serious poisoning.

(5) Purpura, particularly bleeding from the mucous membranes, was relatively rare, being absent in some severe cases.

(6) In severe poisoning the blood may show changes like those in pernicious anemia. Erf and Rhoades[18] noted a feature of benzene intoxication, which may prove helpful in distinguishing it from pernicious anemia, namely, that free hydrochloric acid is present in the gastric juice.

(7) An aplastic marrow is not typical of benzene poisoning; hyperplasia may be found even more often. In 16 cases, 12 men and 4 women, the 4 women all showed aplasia, but only 2 of the 12 men; the other 10 showed hyperplasia.

This seems to point to a tendency of the male to react with hyperplasia, of the female with aplasia and suggests that the belief that women are more susceptible to benzene than men may be based on the failure hitherto to recognize the hyperplastic form of the disease.

(8) A study of the hyperplastic cases reveals what may be called a neoplastic tendency, rapid growth as shown by mitotic figures, the development of cells having no counterpart in normal tissues but common to a variety of malignant tumors. In a case seen by one of us (R.G.J.) the marrow was full of mitotic figures, and there were occasional giant cells with monstrous nuclei, suggesting a neoplastic tendency. A close similarity between these hyperplastic marrows and those described by Martland[202] in chronic radium poisoning was noted, and in both cases there is a prolonged latency and a tendency to progress for months or years after exposure has ceased.

The influence of benzene on the course of infections in animals has been reviewed. Clinical cases confirm these facts. Thus Rohner and his colleagues[266] noted as an outstanding feature the decided lack of response on the part of their patient to infection. Of Hunter's[18] first 4 cases, those that died had septic temperatures, as did Selling's first case, but the 2 that recovered did not. Meda[216] reported a case of prolonged suppurative cysto-pyelonephritis; Smith[294] reported one of obstinate suppuration of the axillary lymph nodes, another of abscess in the thigh. Severe lesions of the mouth are the most frequent manifestation of this action of benzene, and Vincent's angina was noted in several cases. Martland (see reference no. 118) saw osteomyelitis of the lower jaw and gangrenous stomatitis. Loewy's[192] case was one of death from gangrenous osteomyelitis of the jaw and gangrene of the lungs.

It is probably true of working people poisoned by benzene, as it was of the early cases of radium poisoning, that a diagnosis of Vincent's angina or osteomyelitis was made in many cases without inquiry into a possible occupational cause.

The use of benzene has increased not only because of the demand for toluene for explosive production, but because the new method of distilling petroleum at a great heat, "cracking"#, results in a gasoline or naphtha containing coal tar bodies, benzene among them, sometimes in a high proportion. The manufacturer may believe he is using a safe solvent free from benzene, when actually there is a dangerous amount of benzene present.

The American Standards Association has pronounced 100 parts per million to be the maximum allowable concentration of benzene.

Cracking petroleum means heating it above its decomposition point in order to "crack" or break up the large molecules of the heavy hydrocarbons to form smaller molecules of the lighter. Aromatic compounds begin to appear at 800° F. and at 1,000° F. the amount is appreciable.

Toluene (Toluol): Methyl Benzene and Xylene (Xylol): Dimethyl Benzene

The textbooks say that toluene is a stronger narcotic than benzene, but that is based on animal experiments with measured quantities of vapor. In practical life the greater volatility of benzene makes the danger of narcosis much greater than with toluene or the still heavier xylene. In fact it is very rare to hear of a case of acute toluene poisoning of any severity, still rarer of xylene poisoning.

As for chronic poisoning Batchelor (see ref. 341) of the Public Health Service tested toluene, xylene and that mixture of higher homologues called solvent naphtha or hi-flash naphtha and failed to produce in any of the animals the severe anemia and leucopenia of benzene poisoning; nor did Winternitz[342] find a loss of defensive bodies in the blood. In Selling's[256] experiments with toluene there was destruction of leucocytes but far less than with benzene, and it was compensated rapidly. Hektoen[135b] found no marked changes in the bone marrow or in the absolute or relative white count.

According to Cushny[47] toluene is oxidized in the body to benzoic acid and then, combined with the glycocol of the body, it is excreted as hippuric acid. Benzene is oxidized to phenol and dioxybenzol, which combine in the kidney with sulphuric and glycuronic acids to form conjugate acids and the corresponding dioxy compounds.

Nevertheless from all the industrial countries, Germany especially, come contradictory reports concerning the two methyl derivatives of benzene, some asserting the safe character of these solvents, others the contrary. Reports have appeared from England and from Germany with claims that toluene and xylene have been proved to exert an action on the blood forming tissues which differs not at all from that of benzene. Most of the German cases were in printing establishments, probably in rotogravure work, where large quantities of xylene or xylene and toluene seem to be used[302,236]. For instance, there is the case of a lithographer, who was exposed for a long period to xylene fumes, and died of aplastic anemia. The autopsy showed severe damage to the bone marrow, atrophy of lymphoid tissue and complete atrophy of the normal cellular elements in spleen and lymph nodes. There were also 12 cases of poisoning in German color printers, who showed leucopenia and thrombopenia but in only 2 cases a reduction in red cells. Here, however, benzene was used in addition to the other two. Gerbis, who has had a long experience in the German factory inspection service, says that the cases in the printing industry are severe in proportion to the amount of benzene present in the solvent, and that toluene and xylene are far less harmful. One of the recent series of experiments on blood changes from these two homologues was reported by Engelhardt[67], who found a decrease in the number of red cells after exposure to high concentrations, a proportionately lowered hemoglobin, a

marked leucocytosis and a considerable fluctuation in the proportion of lymphocytes to polynuclears. These are, of course, far less severe changes than those caused by benzene. So far Ferguson and his colleagues[74] are the only ones who insist that toluene and benzene have an identical effect on the blood. They tested the two on rabbits and rats and found that, while benzene is the more toxic, probably because of its greater volatility, the effects of the two on the blood forming organs are similar, first stimulating the formation of young blood cells, then producing leucopenia, anemia and thrombopenia. They also describe a case of agranulocytic anemia in a workman exposed to toluene (see also R. H. Wilson[340]). Smyth and Smyth[297] observed in experimental toluene poisoning signs of early toxic damage in the cells of liver and kidney and some pulmonary inflammation but only after inhalation of heavy fumes.

The authors of this chapter have had confidential communications from several industrial physicians who have had disappointing results following a change from benzene to toluene. Instead of a disappearance of the leucopenia and anemia there was little if any change in the blood, in one instance even after the lapse of 3 years. In fact not only did the low counts persist, but some women, whose blood counts had been normal at the time benzene was discontinued, developed polynuclear leucopenia and low red cell count and low hemoglobin while working with toluene. This is a puzzling situation. One does not know whether to assume a persisting action of benzene even after exposure has ceased or a combined action, the toluene continuing the damage begun by the benzene. A striking instance of this is a case of fatal aplastic anemia reported to one of us (A.H.).

A leather worker was exposed to benzene continuously from 1918 to 1928 and thereafter was exposed to a substantial quantity of toluene vapors from 1928 to 1931, when he was disabled and six months later died of aplastic anemia with typical blood changes. The autopsy was performed by Martland, who found an aplastic marrow, and the award was rendered in favor of the widow and dependents on the ground that exposure to toluene can produce chronic poisoning or aggravate a benzene poisoning previously acquired.

A number of mass observations of workers exposed to toluene have been made in recent years. Greenburg and his colleagues[103] examined 106 painters and a control group of 430 fur workers. The concentration of toluene in the workrooms ran from 100 to 1,100 parts per million. Sixty-one painters had had no exposure to other solvents; 45 had had exposure to other solvents, 30 of them to benzene. The comparison with the controls ran as follows; enlarged liver, painters 30 per cent., controls 7 per cent.; in the 61 with no previous exposure, only 21.4 per cent. had enlarged liver, but even this is three times the control rate. There was in the painters' group a slight decrease in the red cell count and

a slight lymphocytosis; the mean corpuscular volume was somewhat increased in 23.6 per cent. (controls 7.2 per cent.); the hemoglobin was higher; values of 16 gm. per 100 or more were found in 37.7 per cent. as contrasted to 2.4 per cent. of the controls. All these deviations from the normal were slightly more marked in men who had had previous exposure to benzene.

The Public Health Service[243] tested concentrations of toluene from 50 to 800 ppm (parts per million) on three normal subjects and concluded that inhalation of 200 ppm for 8 hours causes slight but definite impairment of coördination and reaction time, which is liable to increase the danger of accidents; with higher concentrations these effects increased and at 600 to 800 ppm they could be observed after a few hours' exposure. The elimination of hippuric acid in the urine increases with the concentration of toluene in the air, but the ratio of inorganic to organic sulphates is not affected by toluene, nor was there any sign of injury to the blood forming organs.

The latest study of toluene exposure in a large group is that of Rex H. Wilson[340], who was able to follow the history of some thousand employees working with commercial toluene for one to three weeks in concentrations from 50 to 1,500 ppm. One hundred showed symptoms severe enough to send them to the hospital for examination, and 10 of these showed blood changes. There were no deaths. Those exposed to concentrations no higher than 200 ppm. were practically unaffected; at 200 to 500 ppm headache was complained of, and there developed nausea, anorexia, bad taste in the mouth, lassitude, slight but definite impairment of coördination and reaction time, but no significant physical or laboratory findings were noted. When the concentration of toluene was over 500 ppm, all the above disorders were increased, sometimes markedly, and in several cases petechial hemorrhages appeared under the skin.

In most of the cases the blood picture was normal except for a fall in the red cell count, usually down to 2,500,000. Leucopenia was found in only 2 cases, with white cell counts 2,500 to 3,000; here all the other blood elements were reduced, and biopsy of the bone marrow disclosed partial destruction of the blood forming elements.

In dealing with commercial toluene and xylene, it must never be forgotten that both are very likely to contain benzene. The ordinary method of distilling these bodies does not make for their complete separation, nor is it necessary in industrial use to have pure products.

The maximum allowable concentration for toluene has been set by the American Standards Association at 200 ppm (parts per million), for xylene at 200 ppm.

Benzene Derivatives

The derivatives of the benzene ring are numerous; they are industrially important, and they are of course extremely complex. New ones are introduced continually, too rapidly to allow the toxicologist to keep pace with the chemists, who produce them, and as a result we have here a most obscure and difficult field for the industrial physician. Sometimes it is possible to predict from the chemical composition of the simpler members of the coal tar group what the physiological action probably will be, although even here the problem of the isomers enters, for of three compounds with the same formula the one in the para position may differ in its action from the one in the ortho position and both from the one in the meta position. Thus the toluidins are toxic in this order; para first, then ortho, then meta. The French high explosive, melinite, is a mixture of trinitrophenol and of the isomer of dinitrophenol which has the two NO_2 groups and the HO group attached to the ring in the 1-2-4 position. This isomer proved during World War I to be highly toxic with a characteristic action which was not shared by any of the others. Later on, its use as an anti-obesity drug amply confirmed the French observations. There is also a decided difference in the toxicity of substitution products formed by displacement of the hydrogen in the ring and those formed by displacement of hydrogen in a side chain. An example of the former is toluidin, which is very toxic, of the latter, benzylamine, which has the same written formula but is fairly harmless. Many other illustrations could be given, but these are sufficient to indicate some of the complexities of the subject.

According to Fraenkel[81] the entrance of the HO nucleus to form the phenols, naphthols and cresols increases toxicity, but industrially these bodies give very little trouble except in the matter of burns with a very rare case of extensive skin absorption followed by collapse and death. The entrance of chlorine into an aliphatic compound increases its toxicity, but the reverse is true of an aromatic compound. The chlorbenzenes are less toxic than benzene. The nitroso group and the nitro group always increase toxicity, but when a nitro compound is reduced to an amino, as when nitrobenzene is reduced to aniline, the toxic characteristics remain much the same, but the intensity of action is lessened.

Aniline: Nitrobenzenes: Nitrotoluenes

According to some authorities all of the clinical manifestations of poisoning by the nitro and amino benzene derivatives may be explained by the formation of methemoglobin and the resulting oxygen starvation, but in very rapid and severe poisoning a direct action on the central nervous system takes place before methemoglobin is formed (Heubner[137]). Clark, van Loon and Morrisey[42] testing ani-

mals with aniline decided that the most important action is the formation of methemoglobin, with resulting anoxemia and depressant action on the central nervous system which is specially sensitive to anoxemia. With this Young and his colleagues[351] agree but add a direct toxic action as shown by a marked fall in blood pressure and cardiac arrhythmia.

The effect on the bone marrow is at first to stimulate active red cell production as shown by polycythemia, although sometimes with low color index, and then inactivity follows. There are evidences of effort at regeneration, stippled red cells, polychromatophilia, nucleated forms, variation in size and diminished platelets. An early leucocytosis is followed by a lymphocytosis. The blood often is chocolate-colored and appears thicker than normal. It may be impossible to make hemoglobin estimations by means of color scales, for the methemoglobin changes the color of the blood.

The smoky or dark brown or port wine color of the urine is noticed by the men themselves as an early sign of poisoning. Hemoglobin has been demonstrated in the urine, also hydrobilirubin and hematoporphyrin. A reduction compound is found in the urine in some cases and serves as a proof that absorption is taking place. These are para-amino phenol from aniline, the nitrobenzenes and nitroanilines, amino-2-nitro-4-phenol from dinitrophenol, dinitro-hydroxylamino toluene (Webster test[227]) and 2.6-dinitro-4-aminotoluene (Snyder and von Oettingen test[299]) from trinitrotoluene.

Certain of the nitro and amino compounds are conspicuous as causes for occupational poisoning. Thus the British factory inspectors list cases almost every year from exposure to the intermediates, DNB, DNT and TNT, from the making and use of aniline, from aniline-black dyeing and from dinitrochlorbenzene. " Anilinism " is the term under which these cases are listed, and under this term reports have been made since 1930.

Some of the histories show clearly that skin absorption plays an important part in such poisoning. For instance a workman carrying a bucket of aniline slipped and splashed it over his coat and arms. He took off his coat and washed his arms, but then put on his coat again. Some hours later he become cyanosed, was dizzy and drowsy and, when removed to the hospital, was only semiconscious.

A case which illustrates this point was seen by one of us (R.T.J.). This was in a chemist's assistant who spilled nitrobenzene on his trousers and almost at once fell to the floor. He was rushed to the hospital in his soaking clothes and was unconscious when he arrived with respiration at first rapid, then slow and irregular, pulse feeble, heart sounds distant and weak, cyanosis marked. A sample of blood was of a deep brown color. He died an hour and a half after the accident. Postmortem examination revealed nothing of note.

Volatile liquids such as aniline act more rapidly than solids, as for instance

trinitrotoluene. When poisoning is slower, there is a toxic action on bone marrow and liver, and acute degenerative hepatitis may result with or without aplastic anemia. TNT is the substance which has given rise to the great majority of such cases in the literature, but an unusually slow form of dinitrobenzene poisoning has been known to result in the same liver lesions.

Prosser White[329] has described dinitrobenzene poisoning as he saw it in British explosives manufacture in World War I. The poison passes rapidly through the skin and also is inhaled as vapor. A workman, who breathed for ten minutes the air in a flue through which pure dinitrobenzene had been poured from the mixing pans, died eighteen hours later from the effects. Such cases were rare, but chronic poisoning was far from rare. This was characterized by a severe form of anemia, the skin was dusky yellow, the conjunctivae jaundiced, the man looked as if he were suffering from partial asphyxia, his muscles were wasted, sensation dulled, paresis of the hands was marked, there were paresthesias, hyperesthesia and defects of vision.

Almost all of the compounds of this series seem capable of setting up a more or less severe dermatitis, although some are far worse than others. According to White[329] the intermediates, which are responsible for lesions of the skin, are the following in the order of their injurious action; dinitrochlorbenzene, dinitrophenol, p-nitrosophenol, p-nitrosocresol, diaminophenol, p-nitroaniline, p-aminophenol.

Dinitrophenol

Dinitrophenol 1-2-4 or alpha dinitrophenol was a constituent of the French explosive melinite and is also an intermediate in dye production; for a while it came into use in the treatment of obesity. It is a powerful stimulant to metabolism. According to the French investigators, Etienne Martin and A. Meyer (see Perkins[253]), the mechanism of intoxication consists in an enormous increase in the intracellular oxidation processes with consequent increase of gaseous exchange from ten to twelve times the normal and rise of body temperature in spite of the distension of skin capillaries and profuse sweating. This excessive oxidation affects metabolism and nutrition and damages liver and kidney cells. Unchanged dinitrophenol and the reduction products, amino- and diamino-nitrophenol, are found in the urine. There are absolutely no pathological findings at autopsy.

The use of alpha dinitrophenol for the treatment of obesity has led to a number of cases of serious poisoning with symptoms such as those described above and in 4 cases with agranulocytosis (see Silver[289]). The pronounced toxicity of this compound should lead to great caution in its industrial use, which unfortunately is increasing.

Dinitrocresol

Another compound of increasing importance in industry is 3.5-dinitrocresol, which has an action similar to that of dinitrophenol, being in the opinion of some observers less toxic, of others more toxic. It has been used also in the treatment of obesity and has been responsible for severe and even fatal poisoning (von Oettingen[242]). Industrial poisoning has been described by a German (Schwarz[280]) and recently by J. M. McDonald[211] of the Bureau of Occupational Diseases of the Baltimore City Health Department. McDonald's case was in a negro, whose palms and soles were dyed a deep canary yellow, and who recently had lost 20 pounds. He had a temperature of 102° F., a phenomenal basal metabolism rate of 400 plus, rapid pulse, rapid respiration, profuse sweating, shortness of breath and cough. An examination of his work place showed he had been exposed to 4.7 mgm. of dinitrocresol dust per cubic meter of workroom air per day. The man recovered.

Paraphenylenediamine

Paraphenylenediamine is used very generally as a dye for furs, known in industry as ursol. It is a notorious cause of dermatitis both in fur dyers and fur wearers, and also it has been known to set up in susceptible individuals typical attacks of bronchial asthma, which are attributed by Hanzlik[125] to direct irritation of the air passages, by Mayer[204] and others[29] to an allergic reaction.

Nitroanilins, para and *meta,* are important intermediates in dye manufacture, and cases of severe poisoning have been reported following overexposure to fumes or dust. The symptoms are characteristic of the aniline group as already described.

Chlorotoluidine

An amino compound, 5-chloro-2-toluidine, has caused a good deal of trouble recently in some English factories, the intoxication being characterized by cyanosis, tachycardia and hematuria with subsequent albuminuria, strangury and frequent micturition. The bladder is affected chiefly, the kidneys more slightly. For further discussion of this and for the 4-chloro and 6-chloro isomers see von Oettingen[242].

Betanaphthylamine

The *amino derivatives of naphthalene* are important dye intermediates and have been the subject of much study because of the part one of them, *betanaphthylamine,* plays in the production of bladder tumors. In the experience of one of us (A.H.) both are capable of producing symptoms of "anilism", but in

practice the alpha isomer gives little trouble, while the beta may cause cyanosis and frequent micturition from the presence of the carcinogenic substance.

Trinitrotoluene: TNT

This was studied exhaustively during World War I, especially by the British, and experience during World War II has not added much to the facts accumulated in 1914–18. It is highly toxic both locally and after absorption. It produces a sago-grain dermatitis, intensely irritating with exfoliation, appearing on hands and forearms chiefly but wherever the skin is exposed or touched with TNT smeared fingers. In American plants there was invariably an increase of dermatitis in hot weather, not only because arms and necks were more exposed, but because the sweat helped to dissolve the TNT dust and quicken its absorption. Because TNT is absorbed through the skin, the mixture of nitrate of ammonia and TNT, known as amatol, is more productive of poisoning than pure TNT. Ammonium nitrate is hygroscopic and keeps the skin of hands and forearms moist, thus dissolving the TNT.

TNT belongs to the group of poisons which enter through the skin, and which form methemoglobin[317]. Cyanosis is a characteristic symptom. The usual case of "TNT sickness" shows pallor, bluish lips and lobes of the ears, breathlessness, feeling of tightness in chest, abdominal pain, nausea, headache, lassitude, anorexia. Jaundice is a serious sign of liver damage, and no worker, who has recovered from such an attack, should ever be exposed again (Hilton and Swanton[139]). TNT affects the liver, the bone marrow and the vascular endothelium in varying degree[199]. Severe intoxication therefore results, in acute toxic hepatitis, toxic purpura and more rarely, aplastic anemia. Evans[69] reports 7 cases of TNT jaundice with 3 deaths. Autopsy revealed acute yellow atrophy of the liver and hyperplastic bone marrow.

A recent article (March, 1944) by Coyer[44] reports 7 cases of TNT poisoning of the gastrointestinal type, one of them fatal. In this case autopsy revealed severe jaundice, cirrhosis of the liver with superimposed hepatitis and hemorrhage into the gastrointestinal tract.

In World War I physicians in charge of TNT plants depended on the Webster test[227] to give warning of approaching danger. This color test revealed the reduction product. It is, however, proof only of absorption. Kennedy and Ingham[161] prefer a simple test for the determination of porphyrinuria, which shows intoxication. Snyder and von Oettingen[299] propose a new test more sensitive than the Webster test for a reduction product in the urine, which they tentatively identify as 2.6 dinitro-4-aminotoluene.

Experience in England indicates that women are more susceptible than men

to TNT, colored men less than white. The greater susceptibility of youthful workers was demonstrated in American plants during World War I[116].

Tetryl

Tetryl is trinitrophenylmethylnitramine, a very important military propellant. Tetryl dermatosis was recognized during World War I as a very troublesome affection, but it was believed that this was the only form of poisoning to be looked for in tetryl workers. More careful studies made during 1943 reveal the fact that systemic effects also may occur. Witkowski and his colleagues[345] report no less than 1,258 cases of industrial illness due to tetryl in a force of over 5,000 workers. The chief complaint was of a dermatitis, usually on the face and neck. Epistaxis was a common complaint, and small ulcerations of the nasal mucosa furnished the cause. A systemic effect was seen also. Anorexia, mild nausea, flatulence and abdominal cramps occurred in 10 per cent. of all exposed; dry cough and pain in the chest, headache, irritability, sleeplessness, lassitude were frequent complaints. Three cases were serious enough for hospitalization. All had a history of severe tetryl dermatitis, which recurred with increased intensity on a second accidental exposure. The authors emphasize also the occurrence of rapidly developing secondary anemia. Noro[238] of Finland observed anemia in 109 of 163 tetryl workers.

Chlor Compounds of Benzene: Nitrochlor

Chlor compounds of benzene are used largely in industry, notably paradichlorbenzene, which is a constituent of drugs, anti-moth mixtures, insecticides, etc. It gives rise to dermatitis, but if systemic symptoms arise in a sprayer of this compound, it would be well to learn what is the liquid vehicle, for it might be benzene, carbon tetrachloride or carbon disulphide.

Nitrochlor compounds are more irritating to the skin than those without the nitro group, and they produce systemic poisoning with methemoglobinemia of like character but less severe than that of nitrobenzene (von Oettingen[242]).

Diphenyls

Diphenyl, an important intermediate for the newer plastics, is two benzene rings linked together and is made by bubbling benzene through molten lead. At ordinary temperature it is solid, which may explain why no trouble has been reported from its use. This is not true of its important chlorine derivatives.

Chlorinated diphenyls are used for the same purposes and often in conjunc-

tion with chlorinated naphthalenes. In their study of the latter Drinker and his colleagues[55] tested also chlorinated diphenyls and chlorinated diphenyl oxides. They found that the former bodies act much as do the naphthalenes of low chlorine content, and that the same limit of concentration in the air may be permitted, 100 mgm. per 10 cubic meters of air. For the chlorinated diphenyl oxides the limit should be the same as that for the higher chlorinated napthalenes, 50 mgm. per 10 cubic meters. Greenburg[99] has outlined the proper methods of protection against injury from these compounds.

Aniline Tumor of the Bladder

An interesting and long unexplained manifestation of slow chronic poisoning by coal tar derivatives is the so-called aniline tumor of the bladder, a papillomatous growth which undergoes carcinomatous degeneration. The German dye industry, since it is the oldest and much the most extensive, was the first to discover that men in contact with certain dye intermediates suffered in abnormal proportion from cancer of the bladder. By 1920 the reported cases numbered 177, and each year new ones have been added. Animal experiments were not fully convincing, but it was soon established that whatever was the elimination product in the urine responsible for these tumors, it belonged to the amino group, not the nitro. Hueper and his colleagues[143] succeeded in producing neoplastic lesions of the bladder in 9 of 16 dogs treated with beta-naphthylamine. Morigami and Nisimura[228] had a like success with orthotoluidine and benzidine. Cases develop chiefly in men exposed to aniline, benzidine and beta-naphthylamine, but other amino compounds also have been accused. Usually it is only after an exposure of many years that the tumor appears, and in some cases not until years after all work with amino compounds has ceased.

In England the first cases of aniline tumor of the bladder appeared much later than in Germany because the industry is of more recent origin (Wignall[331], Macalpine[194]). According to Legge[183] 23 fatal cases had been reported in England up to the end of 1931. In the United States the manufacture of coal tar dyes did not amount to much before the outbreak of World War I shut off the supply from Germany. Twenty years later the first American publications on aniline tumors of the bladder appeared in the shape of a number of articles by the group of physicians associated with the E. I. du Pont de Nemours Company (Ferguson and associates[75]). In the experience of these men the active agents have been benzidine or beta-naphthylamine or alpha-naphthylamine containing about 5 per cent. of beta. The unusual feature of this report is that it is based on 532 cystoscopic examinations, which enabled the physicians to discover 25 positive cases, or 4.5 per cent., and 16 others with hemorrhagic areas in the bladder.

The age of these men varied from 30 to 60 years and the exposure from 4 to 18 years. Of the 25 tumors 14 were simple papillomas, 8 carcinomas, and 3 were doubtful.

Neither the Germans nor the English use cystoscopic examination as a routine measure, believing that the workmen would not submit to it, so they are obliged to depend on the detection of blood in the urine. After blood has been found three times the cystoscope is used. Gehrmann[75] of the du Pont Company is convinced that a cystoscopic examination should be made once a year in all men exposed to the dangerous compounds and immediately, if blood appears in the urine. They no longer shift positive cases to other work, for the German experience has shown that once a man has been exposed removal does not lessen the danger to him and only results in the exposure of a new man. Even if a workman is discharged, he should be given an examination at least once a year thereafter, if he had worked with the tumor-producing compounds.

Aniline Dyes

The substances used in the production of coal tar dyes, to mention only the toxic ones, are the " crudes ", benzene, toluene, xylene, phenol, which are treated with mineral acids, alkalies and certain compounds of the aliphatic series such as methyl alcohol, dimethyl sulphate, formaldehyde, methyl chlorides; reduction is effected by means of nascent hydrogen produced from zinc and hydrochloric acid in the course of which AsH_3 may be given off, nitration by nitric acid and oxidation by potassium chlorate and lead peroxide. The resulting compounds, known as " intermediates ", are chiefly nitro, chlor and amino compounds[322]. Reduction is now being replaced by amidation in some plants. Aniline can be produced by amidation of benzene with ammonia, and this process does not carry any danger from AsH_3.

The finished dyes for the most part are quite harmless, and the dermatoses that sometimes appear in dye makers and dyers should be attributed to over-harsh methods of cleaning the hands (White[329]). Commercial aniline, which may contain nitrobenzene, has been used for printers' ink, hair dyes and floor polishes, but such uses are rare now. A new use, however, for aniline is as a stabilizer of trichlorethylene in degreasing tanks to prevent the break up of tri with the formation of metal-corroding hydrochloric acid.

Carbon Disulphide

Carbon disulphide for many years has played an important part in the rubber industry in Europe and a less important part in American rubber manufacture.

It is necessary to incorporate sulphur in crude rubber, the process being known as vulcanizing, and this may be done either by adding flowers of sulphur and then heating the mass, or by exposing rubber to the action of sulphur monochloride either in vapor form, or by dipping it in the liquid or by painting. The carrier for sulphur monochloride usually was carbon disulphide. American manufacturers always have preferred the heat cure for rubber, while the Europeans preferred the so-called cold cure with carbon disulphide. It is this last compound that has given to European rubber manufacture a very bad reputation, and the literature is full of reports of carbon disulphide poisoning in rubber workers. Recently these cases have diminished in number as hygienic conditions have improved, but their place has been taken by a new class of workmen, the makers of artificial silk by the viscose process. This is the process used in Europe and the Orient and also in this country in the production of " viscose rayon ".

Carbon disulphide was recognized as an industrial poison by the French almost one hundred years before psychiatrists in the United States were willing to do so. Payen[248] who first described its action in 1851 was followed by Delpech[51] in 1856, the latter describing 24 cases in rubber workers and also experimental poisoning in dogs. Germany followed with a number of very thorough studies of this poison, whose manifestations were said to be as varied as those of lead (Koester[170]). Then many reports began to come from Italy[264], some from England, France[235], Holland, Japan, but up to the early years of this century only one article had been published in the United States, that of Peterson[255] in 1892 describing carbon disulphide poisoning in rubber workers.

Recently the picture has changed markedly, and there are now a number of American publications on the clinical and biochemical action of this poison on viscose rayon workers and on experimental animals. The most important of these are contained in a series of studies, clinical, anatomical and experimental, conducted by a group of members of the faculty of the University of Pennsylvania Medical School under the leadership of F. H. Lewey[252]. These are based on an examination of 120 men employed at the time in those processes of rayon manufacture, which involve exposure to fumes of carbon disulphide, and on experimental intoxication of animals[188]. Mild forms of poisoning were found in nearly 60 per cent. of spinners, whose exposure is not high, while in churners, whose exposure is much higher, severe poisoning was found in 20 per cent. in one plant, in 44 per cent. in the other.

Lewey and his colleagues found that chronic carbon disulphide intoxication may involve all parts of the central and peripheral nervous systems, beginning with psychic symptoms, later peripheral neuropathy and damage to the cranial nerves, decrease of corneal and pupillary reflexes as well as pyramidal and extrapyramidal signs. Varying degrees of Parkinsonism were observed also. All these

had been described already in the foreign literature, especially by Germans and Italians.

The commonest form of carbon disulphide poisoning is neuritis[187], which may affect any of the nerves but most commonly involves the nerves of the limbs and certain of the cranial nerves, optic, auditory. Both the motor and the sensory nerve fibers are affected, causing abnormal sensations and loss of power. For evidence of sensory involvement we must depend on the patient's word, but motor nerve injury is revealed by objective tests of known reliability.

Usually the trouble begins with a sensation of crawling over the skin, formication, a tendency for the arms and legs to " go to sleep ", a sensation of coldness and heaviness and a curious feeling that the hand and foot belong to someone else. Pain is associated with these symptoms and tenderness along the nerve trunk, and at the same time tests may show touch, pain and temperature sense to be heightened, rarely diminished.

Sometimes irritative symptoms prevail, constant or paroxysmal pain in the distribution of one or several nerves or sometimes generally diffused. During the night pain in the legs may reach an intolerable intensity. Aching muscles, cramps and sharp pains shooting up and down the legs may make sleep impossible.

Any of the nerves may be affected, but those more usually involved are the radial and ulnar in the upper limbs, the sciatic and external peroneal in the lower. Lewey's group found that areas supplied by the anterior and lateral cutaneous nerves of the thigh often were the seat of hypersensitivity.

These symptoms are followed soon by signs of motor nerve involvement. Lewey's group found such signs more frequently than those of sensory nerve injury. The victims complained of early fatigue, gradually increasing loss of strength and especially difficulty in climbing stairs or walking up hill. Weakness in the legs appears earlier and is complained of more frequently than weakness in the arms. Some observers have found the extensor muscles more severely involved than the flexor; others find the reverse to be true. Sometimes there is an exaggeration of the deep tendon reflexes, biceps, triceps, patellar, Achilles, especially in the early stages, but more often the reflexes are diminished. The muscles are weak, and as time goes on, wasting appears, more or less marked according to the severity and duration of the poisoning. The " chronaxia " test, which measures the time it takes to produce excitation of the nerve-muscle apparatus together with the strength of current required to produce it, was applied by Lewey's group. In a few individuals it showed an increase of electric irritability, but in the majority of cases there was a decrease, sometimes very marked.

Lewey found evidence of peripheral neuritis in 87 per cent. of 120 men exposed to fumes of carbon disulphide. The course of carbon disulphide neuritis

is slow, slower than that of alcoholic, rheumatic or syphilitic origin. Recovery proceeds with extreme slowness, and the prognosis must be guarded, because the atrophy, pain, paresthesias, etc. may persist even if the victim quits his job.

The most striking and the most disastrous effects of carbon disulphide poisoning are upon the brain. The mental symptoms run the gamut from simple irritability and depression to manic-depressive insanity. If the basal ganglia are involved, Parkinsonian palsy occurs. In typical cases the attack of active or violent mental derangement comes on fairly suddenly, but careful questioning of the family and working mates always will bring to light an earlier stage of emotional upset, irritability, depression and complaint of loss of memory. During this stage there may be excessive sexual excitation, which soon is followed by loss of libido and even impotence.

Even in milder poisoning changes in personality are evident, especially in the man's relations with his wife and children, and the victims realize this but are powerless to help it. Sleeplessness, horrid dreams, loss of memory are frequent complaints. Neuritis, shown by weakness, paresthesias, pain, is the commonest form of intoxication by carbon disulphide; disturbances of vision, though rarely of a pronounced character, are present often and give valuable aid in the diagnosis. Diminution or loss of the corneal reflex is stressed by Teleky[22], central scotoma for color, abnormal color vision, loss of visual acuity, paralysis of accommodation, all have been described.

Lewey and his colleagues[188] made a survey of the changes in the nervous system in man and in experimental animals following carbon disulphide poisoning. " A comparison of the two discloses the fact that in the human nervous system one finds scattered changes in the ganglion cells of the cerebral cortex of varying degree, depending on the severity of the intoxication, disease of the basal ganglia and peripheral nerves, and evidence of vascular involvement; in the experimental animal there are more extensive damage to the cerebral cortex and basal ganglia, injury of the Purkinje cells, vascular changes, minor damage to the spinal cord and involvement of the peripheral nerves."

Ferraro, Jervis and Flicker[76] also produced experimental carbon disulphide intoxication in cats. They found the most important lesions to be a diffuse vascular involvement of a productive type, leading to endarteritis, occlusion of the vessel and secondary softening and to diffuse neurocellular changes, ranging from chromatolysis to severe degeneration scattered all over the brain and cerebellum but most evident in the corpora quadrigemina, the cerebellar and vestibular nuclei.

Gordy and Trumper[94] reported in 1940 21 cases of chronic carbon disulphide intoxication in workers in American viscose rayon factories from exposures lasting on an average 10 years. Encephalopathic symptoms were seen in 90 per cent.,

subjective eye disturbances in 67 per cent. with blurring of the disks in 30 per cent; about 75 per cent. had lessened libido, 70 per cent. various degrees of neuropathy affecting the limbs and over two thirds had gastrointestinal disorders. In 55 per cent. the symptoms indicated localized lesions of the central nervous system including Parkinsonism.

Finally Weise[327] has published an extensive investigation of the gastrointestinal diseases of German rayon workers, especially peptic ulcer, to which he was led by observing the large proportion of gastrointestinal cases among rayon and rubber workers in Berlin. Among 100 such cases 66 were from the carbon disulphide departments of rayon factories. Comparing them with other textile workers through sickness insurance records he found that the latter had only an average of 2.1 to 3.2 per cent. cases in a year, while the rayon workers averaged 17.7 per cent. Weise produced marked gastrointestinal injury in animals.

The American Standards Association has established 20 parts per million as the maximum allowable concentration of carbon disulphide.

Synthetic Rubber

Synthetic rubber production utilizes many of the chemical compounds already familiar in connection with natural rubber manufacture, solvents, anti-oxydants, accelerators. The new toxic substances according to Wilson[339] and to Mallette[197] of the Firestone Company, are three, namely, *acrylonitrile* or *vinyl cyanide, butadiene* or *vinyl ethylene* and *monomeric styrene* or *phenylethylene*. The first has been described already under the cyanides. *Butadiene* is a gas at ordinary temperatures, and it must, therefore, be kept under pressure, which makes it unlikely that exposure would occur under usual conditions. It is mildly narcotic below the lower explosive limit, 2.2 per cent. or 22,000 parts per million. The vapors cause irritation of eyes, nasal passages, throat and lungs, sometimes with cough and also a sense of fatigue and drowsiness but no evidence of a cumulative action. Mallette considers that no permanent effect will follow exposure to concentrations below the explosive limit, which have occurred fairly often in the experimental laboratory without harm.

Styrene was tested by Spencer and his colleagues[300] of the Dow Chemical Company, and it was found that vapor concentrations acutely dangerous to animals range from 2,400 parts per million for an 8 hour exposure to 10,000 parts per million for 30 to 60 minutes. Immediate death results from a primary action on the central nervous system, delayed death from pneumonia. In man there is eye and nose irritation, which Mallette believes should be ample warning of danger. He has seen also light narcotic symptoms follow inhaling styrene fumes. Wilson says that a year's exposure to styrene, not over 500 parts per million, does

not result in any sign of chronic disease. The rubber industry has suggested 200 parts per million as a safe limit.

The Public Health Service has tested a fourth compound, *chlorobutadiene*, known as *chloroprene*, the starting point for Duprene rubber. It is toxic to animals, causing severe degenerative changes in the organs, depression of the central nervous system and low blood pressure[244].

Tobacco: Nicotine

The tobacco industry has a very bad reputation, and in all foreign textbooks on industrial disease this is listed as one of the dangerous trades, yet there are surprisingly scanty data on which to base such a belief. The assertion is made often that tobacco workers suffer inordinately from pulmonary tuberculosis, from nervous disorders including dimness of vision, and that women workers have an unduly high rate of pelvic disease. It seems to be true that there is an excessive tuberculosis death rate among tobacco workers even in this country, where the industry is for the most part carried on in excellent, highly mechanized factories, but the cause is not the dust; rather it is the low wage and the fact that tobacco work attracts persons of poor physique (Dublin[57], Landis[179]). Long[193] observed 1,246 tobacco workers over a period of ten years comparing them with a control group of 1,008 and found no evidence that the former group had an excess of pneumoconiosis. He seems to have been the first to use the x-ray and fluoroscope in investigating tobacco workers. Nervous disorders with nausea and vomiting are a common occurrence among the newly employed, but they soon grow accustomed to the effect, as smokers do. Burstein[29] found that workmen in Russian factories breathe dust representing somehat less nicotine than they would absorb by smoking 20 cigarettes. A few cases of blindness from long contact with nicotine have been recorded, but they are not beyond question. An excess of pelvic disease in women tobacco workers seems to be shown by the sickness insurance statistics of Germany and Austria, whatever the explanation may be.

Stevenson[301] has been able to observe acute nicotine poisoning in a California factory, which manufactures insecticides. From a study of 10 cases of acute poisoning and observation of the employees in general he concludes that the symptoms caused by nicotine are not the same as those caused by smoking tobacco, for smokers are no less susceptible to industrial nicotine poisoning than non-smokers. The symptoms show a direct action on the spinal cord, medullary centers and the sympathetic system. At first there is excessive secretion of saliva and tears with watery discharge from the nose; then headache comes on with giddiness, numbness, disturbed vision, torpor and rapid respiration followed in about half an hour by faintness, intense depression, cold extremities, nausea, vomiting and increasing

dyspnea. He has not seen the clonic convulsions described by others. Recovery is rapid, provided the victims are kept strictly at rest. Usually they are able to come back to work in 48 hours. Nicotine can be absorbed through the skin (Wilson[338]).

Radioactive Substances

The use of radioactive substances in industry is very recent and as yet not extensive. The accidental exposure of workers to radiation in mining radioactive ores is much older, but the discovery of the part played by emanations of radium in the sickness and death of these miners was made only lately. Even now the industrial uses of radiation are few, but the injuries, that have resulted in some cases, were so spectacular as to arouse wide public attention and lead to strenuous efforts of control, much as the occurrence of " phossy jaw " in a relatively small proportion of match makers led to a world-wide campaign against the use of white phosphorus.

Roentgen rays may be used industrially either for radiography or for fluoroscopy, but the latter is much better adapted for such purposes and is almost always used. The strength of the rays varies according to the thickness of the material to be penetrated; soft rays will do to show the position of the metal plate in rubber heels; hard rays must be used to reveal flaws in castings. Undoubtedly the chief source of x-ray injury is still the use of these rays in medical practice, although now the proper measures for protection are so well known that instances of serious injury are rare. In industrial use there is far more risk of minor injuries, of x-ray lesions of the skin, since the precautions are likely to be far from perfect, but it is doubtful if there will be cases of such severity as have occurred among radiologists, for the workman has not so strong a motive to keep on at work after he has discovered that it is dangerous. So far the only instances of strictly industrial x-ray lesions that have come to light are skin lesions of more or less severe character. These, which are usually on the fingers, are intensely painful even when quite insignificant in appearance and are very obstinate. As we know from non-industrial cases, such lesions may undergo cancerous change years later (Porter[260]), but as yet no cases of that sort have been reported from industry.

Radium. — This section is based largely on the studies of J. C. Aub[6] and R. D. Evans[68]. According to Evans[68] records show that several hundred people were killed through various types of radium exposure prior to 1930. Since then the number of persons engaged in the industrial handling and application of radium has increased about fifty fold. Radium is formed by the natural radioactive decay of its ultimate parent, uranium, which occurs in commercial quantities in a few isolated mineral deposits. Radium is the fifth in a long series of decay products of uranium.

In its radioactive disintegration radium emits alpha rays. For practical purposes the alpha ray can be thought of as an energetic atomic bullet whose range is about 50 microns in living tissue, and which can do lethal damage to most of the cells traversed along its path. After the radioactive decay of radium by its emission of an alpha ray, the residual is an atom of radon. Radon is the heaviest member of the group of noble gases, helium, argon, etc., and is, therefore, chemically inert. However, physically radon, like radium, is radioactive and emits alpha rays in its disintegration. Each decaying atom of radon experiences seven subsequent radioactive transformations before finally becoming a stable atom of lead. In the commercial use of radium radioactive equilibrium usually is present; then each of the decay products, radon, radium A, radium B, radium C and radium C′, has the same rate of radioactive emission as radium.

The alpha radioactivity of radium in equilibrium with its decay products, therefore, is four times as great as the alpha radioactivity of radium element alone. From the standpoint of toxicity, that is cell damage produced by alpha rays, the decay products of radium are three times more hazardous than radium itself. All salts of radium have the same toxicity as the elemental radium which they contain.

In the preparation of self-luminous compound a small amount of some radium salt, usually radium chloride or radium bromide, is mixed with a binding agent and specially prepared and finely powdered zinc sulphide crystals. The alpha rays emitted by radium and its decay products bombard the zinc sulphide crystals and cause them to emit visible light in tiny flashes, one for each alpha ray. The integrated effect of thousands of such tiny flashes of light per second is that of a uniform emission of light.

Zinc sulphide emits a visible light when irradiated by ultra violet light. For this reason a mixture of zinc sulphide and binder is used also as a fluorescent paint without the addition of any radium to the mixture. This fluorescent paint is applied to a number of the markings of modern military instruments. Consequently a number of dial painting concerns have both " fluorescent " and " radium " painting going on in different parts of the same plant. In safeguarding the health of the radium painters this fluorescent painting is a most fortunate circumstance, because it provides a simple means of rotating personnel between radium and non-radium work.

Industrial exposure to radioactive substances occurs in mining radioactive ores, handling and testing the products of the ores, making up radon seeds and making and applying luminous paint to the figures on time pieces and to parts of apparatus. Such exposure has resulted in pulmonary carcinoma, necrosis of bone, malignant growth of the bone and primary blood diseases of various kinds. Carcinoma of the lungs is the kind seen in miners of the Schneeberg region of Saxon

Switzerland, where the cobalt arsenide ores are radioactive, and for more than a century it has been known that a large proportion of the miners died prematurely of lung disease with wasting. The discovery that the disease was pulmonary carcinoma was made in 1878, confirmed in 1913 and again in 1926[268]. At first the arsenic in the ore was supposed to be the carcinogenic agent, but the later studies attributed this action to the radioactivity of the ore. The same ore is found on the Bohemian side of the mountain, and pitchblende is now mined there. Here also the miners suffer from pulmonary carcinoma[257].

In September 1924 Theodore Blum[17], a dentist, described before the American Dental Association a form of necrosis of the jaw with severe buccal infection in dial painters applying a luminous paint, and he attributed it not to phosphorus but to the radioactive substances in the paint. He was the first to discover the real cause of this affection, which had attracted the attention of other dentists in northeastern New Jersey but had been diagnosed as "phossy jaw" or Vincent's angina or syphilis. In some of these cases there was evidence also of a profound injury to the blood-forming tissues.

The cases of radium necrosis and aplastic anemia among these women dial painters attracted widespread interest and much controversy, from which, however, a clear picture gradually emerged[37]. The chief credit must be given to Martland[200], who not only published the first description of the pathology of this new occupational disease but followed year after year the fate of the women, who had been exposed to the luminous paint, and thus discovered the later manifestations of this kind of radium poisoning. In the early cases, which developed fairly rapidly, there was a rarefying osteitis of the bones of the jaw with sepsis and anemia, usually of the aplastic type. In cases developing later there was necrosis of other bones, the femur and the humerus (Martland[200]), the cranial bones (Flinn and Seidlin[78]). Still later, in 1931, Martland and Humphries[202] reported 5 instances of osteogenic sarcoma among 18 victims of fatal radium poisoning in New Jersey and Connecticut, which would make 27 per cent., while the incidence of osteogenic sarcoma in the general population is only 0.07 per cent. Three former dial painters still living at that time had bone lesions which were very suspicious of neoplasm.

Silvertone[291] says that the actual dose required to produce radioactive cancer is not known, but it is known that for its production there must be either a long, continuous exposure or many intermittent exposures. He does not believe that the radionecrotic tissue becomes cancerous, but cancer may arise in the viable tissue nearby, where degenerative and regenerative changes continue side by side. Both are progressive even after the radioactive agent is withdrawn. The type of neoplasm depends not on the nature of the injurious agent but on the type of

tissue affected. The neoplasm arises in the irradiated tissue, but once established it behaves like any other of similar structure and anatomical site.

As for the blood changes the history of radium poisoning in some of the famous radiologists had shown that such changes might be very varied in character. Martland[201] saw, in addition to cases of typical aplastic anemia, 5 of leucopenic anemia of the regenerative type and von Jagic[153] reported 3 cases of lymphatic leucemia; Carman and Miller[34] one.

When taken into the body, radium behaves biochemically like calcium. A portion of the ingested radium eventually is deposited in the bones. The alpha rays from radium and from its decay products, which build up in the bones, bombard the blood producing centers, the bone building cells, osteoclasts and osteoblasts, and the bone structure.

In chronic radium poisoning, where the body contains 1 to 10 micrograms of radium fixed in the skeleton, there are usually no clinical symptoms until some 5 to 15 years after the exposure. There is often no deviation from a normal blood count, and tissue abnormalities are mild or absent.

Because of the wide variations in body resistances, some patients with only 2 micrograms of radium may be more quickly and more seriously affected than others containing as much as 20 micrograms of radium. Unpublished measurements by J. C. Aub and R. D. Evans now include 7 human cases, in which more than 0.02 micrograms and less than 0.5 micrograms of radium have been carried for some 7 to 25 years without the appearance of any clinical symptoms of chronic radium poisoning. On the other hand, several unpublished cases seen by these workers and others measured by Martland with the same or similar analytical apparatus, have resulted fatally, when the radium burden was between 1.2 and 2 micrograms of radium.

Based on these observations a committee called together in 1941 by the National Bureau of Standards tentatively established 0.1 micrograms of radium fixed in the body as the tolerance value for man. This figure replaces tolerance values of 10 micrograms and 1 microgram recommended by individual observers a number of years ago before adequate physical methods were available for detecting smaller quantities of radium in living persons.

Carbon Monoxide

Carbon monoxide is the oldest of the industrial poisons, for it must have attacked the first men who used heat to break stone for implements or who burned wood with little air to make charcoal. It is formed whenever combustion takes place with insufficient oxygen.

In industries of modern life the chief sources, according to Sayers and Yant, are these:

Blast furnace stack gas	28.00 per cent. CO
Bessemer furnace stack gas	25.00 " " "
Arc furnace, melting aluminum	32.00 " " "
Blasting with dynamite	1.20 " " "
Combustion of dynamite	28.00 " " "
Explosion of TNT	60.00 " " "
Coal gas undiluted with air	16.00 " " "
Carburetted water gas undiluted with air	30.00 " " "
Blue gas undiluted with air	40.00 " " "
Producer gas from coke	25.00 " " "
Producer gas from oil	5.00 " " "
Automobile exhaust gas, average	7.00 " " "

At peak hours of traffic on crowded streets tests have shown an average of 0.8 parts of CO per 10,000 of air. In garages the average was 2.1 parts per 10,000 of air (Bloomfield and Isbell[16a]).

Other important industries in which carbon monoxide gas may be a danger are those which use gas as a source of heat or power, even natural gas, for though it is free from CO, if it burns with too little air, CO will be formed. The production of illuminating gas and of power gas, repair work on pipes, cleaning pipes and flues, all are jobs which carry this danger. Less conspicuous are such sources as bakeries and hotel kitchens, printing plants, laundries, canneries, pressing departments of clothing and of felt hat factories.

As to the quantity necessary to produce symptoms Haldane[111b] put the figure at 100 parts per million, and this has been adopted by the American Standards Association as the maximum allowable concentration for a daily exposure not over 8 hours. For shorter periods, such as occur in the Holland tunnel, Henderson and Haggard[111a] allowed as much as 400 parts per million, and this is permitted also by the American Standards Association for exposure of one hour. The studies of Sayers and Yant[275a] in garages led them to the same conclusions. Haggard and Henderson[136] offer this rule for the determination of the danger point. Multiply the hours by the concentration in parts per 10,000. If the sum is 3, there will be no effect; if 6, a slight effect; marked, if 9 and fatal, if 15. Haldane showed that the same degree of saturation of the blood with CO would follow one hour's exposure to 400 parts per million, if the man were at rest in a normal atmosphere, to 350, if he were at rest in a hot and humid atmosphere and to 250, if he were working hard. Age and sex also have their influence. Women seem to survive a heavy exposure better than men, probably because men breathe more deeply. In experiments with animals, Smith and his colleagues[294a] found that

male rats succumb to CO more quickly than females; young rats more quickly than old; pregnant females very quickly.

Acute Poisoning. — Carbon monoxide is not a poison in the strict sense of the word. It does not directly injure the cells of the body. Haggard[110a] was able to grow nerve cells in an atmosphere of 79 per cent. CO and 21 per cent. oxygen. Of course the gases used and produced in industry, which we call carbon monoxide gas, are often really a mixture. Thus Mayers[204b] and her colleagues tested the effect on red blood corpuscles of pure CO, of automobile exhaust gas and of illuminating gas. The first did not increase the fragility of the cells, the second did and so did the third, to a much greater degree. Haggard's nerve cells died in an atmosphere of 0.1 per cent. illuminating gas, which contained only 21 per cent. CO but also benzol and olefins. The action of carbon monoxide is that of an asphyxiant causing anoxemia, and the starvation of the tissues for oxygen is the basis of the symptoms, both acute and chronic, and of the sequelae which play so important a rôle in this form of occupational injury. This is the explanation for the wide variety of lesions which may follow a severe gassing with carbon monoxide, depending upon the particular body tissue which has suffered damage.

The asphyxia brought about by CO is caused by the affinity of hemoglobin for this gas, which is 300 times as great as its affinity for oxygen, and the resulting combination is much more stable. The asphyxia, however, differs from that caused by suffocation. Haldane showed that the presence of CO hemoglobin in the blood interferes with the disassociation of the remaining oxyhemoglobin, so that a person with anemia of 50 per cent. is better able to utilize the oxygen in his blood than is one with a CO saturation of 50 per cent. A third effect is that reduced oxyhemoglobin acts as a catalyst in the liberation of carbon dioxide; therefore, if there is a loss of oxyhemoglobin by its conversion to CO hemoglobin, the removal of CO_2 may be hindered (von Oettingen and Associates[242a]).

The course of acute CO poisoning was studied by Haldane in a series of self experiments which showed that the effects are most marked in the central nervous system. After the preliminary symptoms of "mountain sickness", increasing headache, dizziness, confusion, nausea, abdominal pains, he passed into a condition like that of acute alcoholism, in which his judgment was lost, but he was unable to realize that his mind was not as clear as ever. The condition may go on to mania. The French have evidently seen many such cases in cooks, for they speak of "folie des cuisiniers", probably caused by the CO from charcoal burning stoves. Even if complete coma is not reached, the victim's power of decision and action is so much dulled that he is incapable of saving himself.

As for the action on the heart Haggard experimenting on dogs saw no direct toxic action on the heart, and Drinker's[54c] studies of fatal poisoning in man gave the same result. In extreme asphyxia the most characteristic effect was heart

block. In young, vigorous men there is often low blood pressure and a dilated heart, sometimes auricular fibrillation but with recovery usually except in the case of the last which is likely to mean a fatal outcome.

Drinker and Cannon[54d] found increased moisture in the lungs at autopsy on victims of severe poisoning and signs of the same in the lungs of unconscious subjects. Almost 10 per cent. of these developed pneumonia (Henderson and Haggard[136]). Chiodi and his colleagues[39a] found depression of the respiratory center in severe CO poisoning and an increase of the cardiac output to as much as one half, when saturation is from 30 to 50 per cent.

Sequelae to Acute Poisoning. — To the physician the most important feature of acute gassing by carbon monoxide is the injury, which may have taken place during the period of anoxemia, and which may produce temporary or lasting symptoms. The literature is full of such instances, and every physician in a steel or mining community must have seen at least one such case, yet their number is really small in proportion to the acute cases. Engel[46], who has had 12 years experience in a large steel works, has seen some 1,200 cases of gassing among blast furnace men but no sequelae either in the central nervous system or in the lungs (also Drinker and Cannon[54d] and Forbes[80a, 80b]). In the author's experience lasting damage from acute gassing is rare considering the number of men who have been gassed, yet some very striking cases have come to light from many different sources.

The studies of Forbes, Cobb and Fremont-Smith[80b] on man and on animals showed that carbon monoxide causes increased congestion of the vessels of the brain with edema and a rise in intracranial blood pressure. Given a weakened condition of the walls of the smaller vessels, it is easy to see how an acute gassing might lead to an apoplexy. Chornyak and Sayers[39c] made extensive studies on animals to determine the neuropathology resulting from rapid CO asphyxia. They found severe perivascular and perineuronal edema, most marked in the corpus striatum, the cortex, the dorsal motor nucleus of the vagus and the dorsal sensory areas of the medulla. In these regions there is extensive damage to the neurons. The animals showed decided variation in individual susceptibility. According to Hill and Semerak[137a] the severest damage to the basal ganglia is found in victims of gassing who have chronic vascular disease. Skolnick[292a] describes a case in which CO asphyxia acted as a precipitating cause of paresis in a syphilitic fireman. That damage to the central nervous system is most marked in the corpus striatum was discovered as early as 1865 by Klebs and abundantly verified since then (Hill and Semerak[137a], Poelchen[258b], Grinker[104a]). Parkinsonism is perhaps the most characteristic sequela, but it is not uncommon to find acute gassing followed by confusion, amnesia and loss of initiative and of judgment and will power lasting for months or for life.

The nuclei of the cranial nerves are rarely affected, but undoubted cases of

sight impairment, sometimes permanent, have been published (Wilmer[337a], Murray[231a], Brose[22c]).

Congestion and edema of the retina and of the disk have been described with resulting blurring, dimness, contraction of the visual fields and defective color sense. The lesion may be central, in the cortical centers, the optic thalamus, the optic tracts. François[83a] found in the literature 2 cases of homonymous hemianopsia which followed CO gassing and added one. In his case the left field defect cleared up, but the right persisted. Four cases of serious visual defects following exposure to CO have been reported to the author. Paralysis of the external ocular muscles was described by Abelsdorff, nystagmus by Strecker and associates[302a].

It must not be forgotten that the most severely gassed victims do not live to demonstrate the damage which has been done.

Drinker and Cannon[54d] in their survey of hospital records of 21,143 cases of acute CO poisoning, mostly non-industrial, found 514 severe cases, unconscious on admission. Of these 116 died. Permanent mental or nervous damage was shown by only 39 of the 398 survivors, and all of these followed long periods of exposure and of unconsciousness. It is rare to see such cases in industry, where severe exposure usually is brief. Only in coal mine disasters are workers exposed for long periods. That is probably why English authorities consider permanent sequelae of CO poisoning characteristic in colliers (Glaister and Logan[89a]).

Glycosuria, noted first by Claude Bernard[12g], is present in practically all severe cases, but this action is common to all asphyxiants and is attributed to the increased supply of adrenin in the blood under the stimulus of the oxygen-lack and the increased supply of blood sugar under the stimulus to the liver by the adrenin. Usually it appears early and lasts only a short time, 8 to 24 hours, but it may not appear till several days after the gassing. That a true diabetes may follow CO gassing was asserted by Lewin[190a], one of the most authoritative experts in this field. Ziesché[352b] reported a typical case in a mason, Rogers[264d] one in a truck driver.

Other lesions, a wide variety, have been reported from all the industrial countries. Polyneuritis (Sanger[270b]), choreiform symptoms (Merguet[217a]), hemiplegia (von Jaksch[153b]), exophthalmic goitre (Baader[9a]), injury to the coronary vessels (Nagel[231b]), increase in blood pressure and basal metabolism lasting 10 years (Weil[325b]), neuritis of the auditory nerve (Alt[1b]), skin necroses, gangrene (Briggs[22b]).

A very interesting case is reported by Johnstone[156], one of severe acute gassing followed by deep coma lasting 10 hours, then complete paralysis of the right side with inability to speak. The condition after 3 years showed improvement of the paralysis but with mental dullness, loss of memory, inability to distinguish his wife from other relatives, speech limited to "yes" and "no".

Chronic Poisoning. — Chronic CO poisoning still is a field of controversy, for although there is generally agreement that it is an actual industrial disease, there is little agreement as to the character and the severity of the symptoms, which may be caused by long exposure to low concentrations of this gas. It is an extremely important subject, for many thousands of workers are exposed in this way. That there is no accumulation of CO in the body is beyond question. It disappears from the blood, usually within minutes or a few hours; for exceptions see Farmer and Crittenden[71d]. Damage is to be attributed to the cumulative effect of repeated doses.

Is tolerance established, as men in industry believe? Haldane[111b], experimenting on himself and his colleagues, found a certain degree of acclimatization, but it disappeared after a short interval. Nasmith and Graham[232a] attributed this to the temporary polycythemia which they found in animals exposed to CO. Killick[161a] succeeded in acclimatizing mice to such a degree that they flourished in an atmosphere which overcame the controls. There was increased blood volume, polycythemia with reticulocytes and enlarged spleen. In man he saw increased resistance, as much as 34 per cent. increase, but with no demonstrable change in the blood. This tolerance disappeared slowly after 18 months.

The clinical picture is very varied, although no more so than is the picture of sequelae following acute poisoning. However, the difficulty in making connection between the symptoms and the exposure to CO is great, because there are no characteristic signs or symptoms. Even the presence of CO in the blood does not prove poisoning, only absorption, although in industrial cases it should have great weight, if at the same time the onset of the illness can be shown to have followed exposure to this gas. In most cases the complaint is of frequent headache, nausea, vomiting, general muscular weakness with increased fatigue and "dopiness". Eurich[67a] described such symptoms together with depression and diplopia in 3 men exposed to exhaust gas from motor cars, and in a fourth the symptoms were so severe as to lead at first to a diagnosis of brain tumor. Mayers[204b] in her examination of garage workers heard complaints of insomnia, irritability, dizziness, ringing in ears, rapid pulse, rapid breathing, tremors, increased reflexes, and noted a pallor disproportionate to the degree of anemia, vasomotor in origin (also Symanski[306a]). Loewy[192a] emphasizes the importance as an early symptom of labyrinthine over-excitability shown by dizziness on rising in the morning and looking up to the ceiling. Baader[9a] agrees and holds this to be an important diagnostic aid.

Among the severer manifestations of chronic CO poisoning are the following; loss of vision, reduced on the right side to counting figures, on the left to 20/30 but with narrowing of the visual field (Thompson[315a]), myocarditis (Ziegler[352a]), pernicious anemia (Berger and Grill[12f]) and Basedow's disease described by several authors as a sequel of acute gassing, by Mahain[195b] as a result of 2 years'

exposure in a patient in whom at the beginning of the third year there were tachycardia, tremor, increased basal metabolism, emaciation but no exophthalmus.

The most extensive studies of chronic CO poisoning have been made by Beck[12a, 12b] together with Sutor. Most of their cases are not industrial in origin, but a number are. Beck calls this a neglected clinical problem. In his latest publication he discusses his findings in examining 279 persons whose living conditions were held to involve continuous exposure to CO. He found evidence suggestive of chronic poisoning in 137. In discussing his observations on 150 victims of chronic poisoning he says that most of the symptoms were those of simple anoxemia, but that others suggested organic lesions of the central nervous system, encephalitis, epilepsy, cerebral thrombosis, multiple sclerosis and tetany. Frequently there would be neuromuscular and joint pains, spasms of voluntary and involuntary muscles, nausea and vomiting, increase of red corpuscles and of hemoglobin.

On the other hand Rossiter[267a] denies the possibility of damage by small, repeated doses of CO, since all damage by this gas comes from anoxemia, and low concentrations of CO-hemoglobin cannot produce anoxemia. The Public Health Service[288b] (Sievers, Edwards and Murray) made a significant report on the effect of working many years, 13 years and 4 months, in the Holland tunnel. The study covered 156 men working in an atmosphere which averaged 70 per million CO. There was no sign of health impairment suggesting occupational disease; the response to standard neurological tests was good; there was a low incidence of tremors. Blood analysis showed CO-hemoglobin greater in smokers; the highest, 13.1 per cent., was in a heavy smoker coming directly from work. Toll collectors, whose exposure is greater, went up to 15.1 per cent., but with no signs of poisoning.

Some doubt is thrown upon such findings by the recent experiments of Lewey and his colleagues[64a, 188a] designed to test the generally accepted standard of 100 parts per million for a working day. This amount in the air leads theoretically in man to a concentration of about 16 per cent. CO-hemoglobin, and the American Standards Association sets the upper permissible limit at 20 per cent. Lewey and associates used dogs exposing them for 11 weeks, 6 days a week, $5\frac{1}{2}$ hours a day to 100 parts per million of CO. The condition of the dogs appeared excellent throughout the experiment, but as early as the 2nd week the electrocardiograph showed changes which persisted, and at necropsy there were signs of degeneration in individual muscle fibres, hemorrhages and necroses in the myocardium. Some of the dogs had shown disturbances of gait and of postural and position reflexes, and at necropsy there were found histological changes in the cortex of the hemispheres and in the globus pallidus of the brain stem, resembling in type and localization those found after acute poisoning but smaller, more scattered and less destructive.

These experiments seem to indicate that the accepted standard of 100 per million may be too high for man as it is for dogs, and that damage may occur, which is too subtle to be revealed by the ordinary physical examination.

Hydrogen Sulphide

Hydrogen sulphide, sulphuretted hydrogen, H_2S, is a toxic gas which, like hydrogen arsenide, has no use in industry, is never deliberately produced, so its presence is always the result of some faulty operation or some unexpected reaction. It is a colorless gas with an offensive odor, but this is not to be depended on, for it occurs at low concentrations, and at high it changes to a not unpleasant sweetish odor. Moreover, the gas has a paralyzing action on the nerve of smell, and in the author's experience this effect takes place quickly. It is soluble in water. Fortunately the lower explosive limit is at 4.4 per cent. by volume in air, which leads to precautions against escape of the gas.

The possible sources of H_2S in industry are many, for it is formed by the decomposition of organic matter and, therefore, may be present in the waste pipes and sewers draining abattoirs, glue and gelatine factories, fur dressing and felt hat factories, tanneries. Sewerage systems are the most notorious sources of H_2S poisoning. According to McNally[213] it was the sewer gas of Paris which led to the first study of H_2S in 1777. That gas is said to contain as much as 3 per cent of H_2S.

Chemical reactions which give rise to H_2S are a part of the production of certain dyes and of sulphides and sulphates. The author has histories of several cases of severe poisoning from H_2S among the pipe fitters, repairers and tank cleaners in dye and chemical works. One man, who lifted the lid off a storage tank of barium trichloride which stood out in the sun, fell dead. Since the gas is soluble in water, it is found in occluded seams in coal mines, formed there by the decomposition of pyrites. This is true also of gypsum mines. Oliver[244a] investigated the Sicilian sulphur mines in 1922 and found records of a number of deaths from this gas. Other possible sources are in caisson work and in cleaning out the oxide beds in illuminating gas works.

Recently an unusual source of H_2S gas was discovered in the course of digging through oölithic limestone in constructing sewer mains in Florida[264b]. Underground streams of water were charged with the gas, and when the depth of the hole reached 16 feet, a man was overcome, losing consciousness, but rescued immediately, he recovered. He had not noticed any odor. Some of the men working in shallow holes complained of lassitude, nausea, short breath and conjunctivitis.

Another unusual accident was reported by Nan, Anderson and Cone[231c]. Here there was a mixture of gases, the source being dross containing aluminum,

arsenic, antimony and sulphur. When water was poured on the hot dross, the contact with metallic aluminum produced nascent hydrogen which led to the formation of AsH_3, SbH_3 and H_2S.

However, the greatest danger is in oil refineries, where "sour crudes" are purified. These come from Mexico and Texas and are rich in sulphur. Yant and Fowler[350a] made a report on the Texas oil fields for the Bureau of Mines in 1926, and Aves[6b] in 1929 described conditions in one of the refineries. In the ten adjoining wells the percentage of H_2S ran from 4 per cent. to 14 per cent. All natural life has disappeared from these fields, and once a sudden shift of wind drove the gas into a corral and killed all the mules. Men have been found lying unconscious out in the open to the leeward of a well or in a ravine or near the pumps or tanks. Aves notes also that the gas acts on the skin, preventing the healing of cuts and scratches unless a gas-tight dressing is applied (also [271a]).

Johnstone[156] describes a fatal case in a man who, exposed to a heavy dose of H_2S in an oil refinery, fell and lay with his face in six inches of water. At autopsy no change from normal was noted except the presence of water in the lungs. In a second fatal case no organic lesions at all were found.

The oil industry is the greatest source of severe, accidental H_2S poisoning, and the viscose rayon industry is the chief source of mild forms from continuous exposure. In the latter industry there is a stage at which decomposition of sodium tri-thio-carbonate occurs with the formation of sodium carbonate and H_2S. This is in the spinning department and the gas is evolved in the spinning bath of warm sulphuric acid ([120]).

Hydrogen sulphide is an irritant to all mucous surfaces and is also an asphyxiant. Haggard[111a] explains the irritant action as caused by the combination of H_2S with the alkali of moist tissue surfaces, forming sodium sulphide which is caustic. The asphyxiant action is no longer attributed to a combination of H_2S with hemoglobin, for as an actual fact that does not happen. H_2S combines only with methemoglobin, and this occurs in cadavers giving rise to the greenish discoloration of the vessels of the intestines. Asphyxiation is caused by paralysis of respiration, for H_2S at first depresses the nervous system, then stimulates it, then paralyzes it. Delayed death is from pneumonia or edema of the lungs, probably set up by the irritant action on the air passages. The conversion of H_2S in the blood to the harmless sulphate takes place rapidly so that, if death is not prompt, recovery occurs with no lasting damage.

The fatal dose is between those of carbon monoxide and hydrogen cyanide. Concentrations between 100 and 400 per million cause irritation of eyes, nose and throat; 500 per million causes, after some 30 minutes, excitement, headache, dizziness, staggering gait, diarrhea and dysuria; anything over 500 per million may cause severe poisoning, even death. A careful study of the conjunctivitis, which is a very common affliction of rayon spinners, has shown that the H_2S in the air

should be kept down to 20 per million by volume, if inflammation of the eyes is to be prevented. The injury to the eyes produced by H_2S is described by Barthelemy[11a] as follows: "intense photophobia, spasm of the lids, excessive tearing, intense congestion, pain, blurred vision, the pupils contracted and reacting sluggishly, the cornea hazy, sometimes with blisters on the surface". Nevertheless the acute symptoms usually subside quickly under treatment and removal from the poisoned air, but severe cases may result in lasting damage, if corneal ulcers occur with scarring.

The American Standards Association has adopted 20 per million by volume as the maximum allowable concentration of H_2S.

A few instances of lasting damage from severe H_2S poisoning have been reported, pneumonia, jaundice, psychic and nervous disturbances (Klein[163a]). As for chronic H_2S poisoning there is little information available. From early French writings one learns of the "plomb des fosses", the colic and diarrhea from which men working in Paris sewers suffer and which resembles that of plumbism. Doremus and McNally[54] say that workmen in daily contact with this gas develop headache, gastric disorder, conjunctivitis and a tendency to furunculosis. Chemists, who use the gas, often are said to become oversensitive to it, suffering from headache, colic, digestive disturbance. But Rodenacker[264c] thinks such symptoms are purely subjective, and Moser[229b] was unable to produce any effect except some irritation of the nasal mucosa in dogs exposed 7 hours daily for 2 months to air with 100 per million of H_2S.

Petroleum Distillates

Petroleum and its distillates, gasoline, benzine, naphtha, petroleum ether, Stoddard solvent, kerosene, are mixtures of hydrocarbons, paraffins, olefins, cycloparaffins (naphthenes), aromatics, containing also impurities of which sulphur is the most important from our point of view. "Straight-run" distillates are produced by ordinary distillation, "cracked" by the use of very high temperatures. The former consist chiefly of paraffins, but Western oils have the more toxic cycloparaffins and olefins and sometimes coal tar benzol and its homologues. Cracked gasoline is richer in all these compounds and may carry a fairly high percentage of benzol. Lazarew[180a] tested the toxicity of benzines from different sources on white mice and concluded that the difference in toxicity depends on the ratio of paraffins to cycloparaffins. The specific gravity to a certain extent is a measure of toxicity.

Not only the composition but the volatility of these distillates determines their toxicity in industrial use. The series runs from high test gasoline distilling at 65° C. to 150° C. and low test distilling from 150° C. to 212° C. to solvents, naphtha, benzine, petroleum ether, distilling between 100° C. and 200° C., and

the low-boiling Stoddard solvent used in dry cleaning, which comes off just below kerosene. Hydrogenated naphthas are produced from cracked petroleum, the object of the hydrogenation being chiefly to reduce the bad odor characteristic of cracked products. They are used as solvents for coatings, especially for synthetic lacquers, and their low volatility makes them much safer than the majority of solvents. Solvent naphtha must not be confused with petroleum naphtha, for it is a mixture of benzol and its homologues.

Although these distillates are narcotic poisons, and it is possible to produce complete anesthesia with a heavy dose, nevertheless they require so much larger a dose than do other industrial solvents, chlorinated hydrocarbons, benzol, etc., and the after effects usually are so slight that one is always pleased when one finds them in use. Unfortunately they are inflammable and, therefore, are more and more yielding to non-inflammables such as carbon tetrachloride, trichlorethylene, etc.

No figure has been agreed upon as the maximum allowable concentration for gasoline. Some states, Massachusetts and California for instance, have decided on 1,000 per million. Machle[194b] says that susceptible persons may experience discomfort at 300 to 500 ppm. Vigdortschik[319b] saw cases of functional neurosis in workers exposed to 110–450 ppm. The Bureau of Mines investigators in 1927 found the odor of benzine detectable at 300 ppm., mild symptoms of narcosis beginning in 50 minutes at 1,000 ppm.; by the time 7,000 ppm. was reached, there was marked unsteadiness of gait in 10 minutes with numbness of the legs. Philip Drinker and his colleagues[55a] used several groups of normal subjects, men and women, and found the latter reacting to a lower concentration than the former. Quite tolerable were atmospheres with 270 to 500 ppm. The point at which neuromuscular symptoms begin they place at 900 ppm.; mild intoxication begins at 2,600 ppm. The vapors are heavier than air.

The susceptibility of human beings varies very much. The Russians[277a] hold that the obese are oversusceptible and that a fatty diet encourages poisoning. Machle has seen refinery workers develop resistance to the fumes, and Lazarew and his colleagues[180b] produced a marked degree of tolerance to benzine fumes, which they attribute to the animals' loss of fat, for the action of benzine is on the lipoids.

The industries in which gasoline fumes constitute a hazard are the refineries and the users of solvents, a long list of which is to be found on another page of this chapter. There are many other sources of possible danger in refining petroleum, chiefly the gases that may be given off in the course of distillation, such as hydrogen sulphide, carbon monoxide, sulphur dioxide, ammonia, chlorine. A complicated clinical picture may be produced by a mixture of one or more of these with gasoline.

Acute Intoxication.— The symptoms are those of a narcotic poison with

nothing especially characteristic. Workers call such an attack a "naphtha jag". There is fullness in the head, headache, blurred vision, dizziness, unsteady gait, nausea, etc. and a typical "morning after". Yet, as is true of alcoholic intoxication, the experience may be enjoyed. On the other hand, some workers become very irritable and quarrelsome. A foreman in a rubber spreading department told the author he always was careful how he spoke to his men toward the end of the day. A group of painters using cheap, quick-drying paint in small rooms complained of what they supposed was lead poisoning, nausea, pain in the navel region, smarting eyes, spots before the eyes, dimness of vision, headache, dizziness. In some cases these symptoms came on first when the man went out into the open air. The paint proved to be lead-free but with benzine and turpentine as the carrier.

Moorman[227a] has noted this fact, which is well known to men in the industry, that the symptoms often increase when the victim reaches the open air. Several such instances were reported to the author. One was that of a rubber worker, who dipped glove forms in a tank of rubber dissolved in naphtha. He felt sick and dizzy and started to go home, but on the way he began to stagger and had to be half carried to the house; not till he was in bed did he lose consciousness.

Massive doses such as occur only through an accident result in sudden collapse, coma, sometimes death. An interesting case was described by Plummer[258a] of acute gasoline poisoning in a lad of 16 years who was cleaning a storage pit in a garage. Found dazed in the pit, he was carried outside when he vomited violently, became delirious and lapsed into coma, which lasted 3 hours, with shallow breathing, weak, thready pulse, contracted pupils and inward strabismus. He made a complete recovery.

In fatal cases no characteristic morbid changes are found; usually the blood vessels of the organs show damage, small hemorrhages; there is bronchitis, edema of the lungs, in a case of Johnstone's extensive pleural effusion, but the changes in the central nervous system are not marked. Briganti and Ambrosio[22a], exposing rabbits to heavy concentrations of low-boiling benzine, found extensive hemorrhagic areas and cell injury in kidneys, liver and adrenals, increased blood cell destruction in the spleen and hyperplasia of lymph follicles in spleen and intestinal tract.

Hemorrhages in the lungs were the most important feature in 2 cases of severe acute poisoning described by Jaffe[152a], and he was able to reproduce this condition in animal experiments.

Chronic Intoxication. — As is true of all the industrial poisons, the study of acute forms is not nearly so important as the study of chronic forms and of possible sequelae of the acute. Some striking instances of the latter are reported in German literature.

Floret[79a] of the Chemical and Dye Works at Elberfeld described 2 unusual

cases. One was in a young girl, who suffered from epileptiform convulsions for a year after an acute poisoning from benzine fumes. The other was in a man, who, while filling cans with benzine, lost consciousness and, when he came to, complained of pains in neck and head. There was great restlessness, stiffness of the neck as in meningitis, high fever and albuminuria. After a few days an erysipeloid eruption appeared over the buttocks, later becoming necrotic, and similar areas appeared in mouth and throat. Floret believes these were caused by the excretion of benzine through the skin. The man died in the fifth week after the accident.

Stiefler[301a] describes a case of epilepsy occurring in a man 21 years of age. He had been emptying a can of benzine, fell unconscious and was taken to a hospital. The following symptoms in addition to unconsciousness were noted; asphyxia, tonic muscle spasms especially of the arms, vomiting and dyspnea. He recovered and was discharged in 10 days. Three or four months later he had his first attack of epilepsy. The attacks were repeated every 4 or 5 months and were typically epileptic. Examination revealed no clinical evidences of organic changes in the nervous system or other organs. The author believes that the benzine so changed the brain as to render it a suitable soil for epilepsy.

The most famous cases of chronic poisoning in the literature are those of Dorendorff[54a] and of Haden[108b]. The first described the nervous symptoms in 4 men engaged in rubber manufacture, who suffered from lancinating pains in the limbs, coldness and numbness in the hands, loss of strength, loss of memory and in one case, difficult speech. Haden's patient was a man, who for 13 months had cleaned lithograph rolls in a trough of benzine using 2 gallons a day, all of which evaporated in a room with no ventilation. He began to suffer the symptoms typical of a narcotic poison after 2 months, and his weakness increased till he took an hour to walk home instead of 15 minutes. He was so drowsy he had to wash his face in cold water to keep awake; his legs felt heavy and cold; he had painful muscular cramps in the arms, and his vision was dimmed. After 13 months had passed, his mentality was dull and confused, his reflexes active; there were tremors of eyelids and tongue. A very unusual feature was the involvement of the liver, jaundiced skin, enlarged and tender liver, urine almost black with bile coloring matter. He improved rapidly under treatment and removal from benzine.

Dorner's[54b] case also belongs in the very small list of reported cases of lasting damage after acute intoxication. This was the result of an accident, a fall into a tank of crude benzine. The man lay for 20 minutes half immersed in the fluid. Dorner saw him 7 months later with motor paralysis of the legs, which Dorner traced to degeneration of the pyramidal tracts.

Kraus'[173a] case, one of motor and sensory paralysis with marked atrophy of all the limbs, was in a garage worker exposed to both gasoline and CO fumes Kraus does not attempt to decide what part each played.

Chronic benzine poisoning is considered by some experienced men as fairly common among industrial workers, but others think it is very rare. Of course there are wide differences in the conditions under which the work is done, so the results of different surveys may not be comparable. The action of benzine is primarily on the central nervous system, and the symptoms are those of a narcotic poison. Hayhurst[130a] examined a group of workers constantly exposed to benzine and lists the following symptoms; headache, dizziness, loss of appetite, dyspepsia, insomnia, nervousness, pains in back, legs and heart region, weakness and dyspnea. These symptoms made their appearance after 3 weeks to several years of exposure. There were also objective signs, loss of weight from 10 to 50 per cent., tachycardia, secondary anemia with leucocytosis, mental depression, stupor, twitchings and tremors.

Quadland[262b] describes a case in a man, who for 13 months dipped shingles in a stain the solvent of which was $\frac{1}{3}$ benzine, $\frac{2}{3}$ kerosene. He complained of diarrhea, gastric upset, attacks of numbness, vertigo, weakness, and he had lost weight as much as 40 pounds. Later he developed cardiac disturbances, paresthesias and "syncopal attacks". Quadland's second case, in a woman, was one of extreme emaciation, a fall in weight from 158 lbs. to 65, extreme nervousness, mentality impaired. The third, a man working with high-test gasoline, had also lost weight, suffered from marked nervousness and in addition had bleeding from nose and gums.

This last manifestation of chronic benzine poisoning, hemorrhagic tendency, comes into the picture in other reports. Koelsch[166a] describes a case of bleeding from the lungs together with albuminuria and anemia. The most remarkable instances are those described by Smithies[295a], partly in a personal communication to the author, where the exposure to "very volatile oil distillates" resulted in several instances not only in hemorrhages but in laking of the red corpuscles. In one of the cases xylol was involved as well as benzine.

The effect of chronic benzine poisoning on the blood still is a matter of controversy. The earlier literature, especially the French and Italian, contains descriptions of aplastic anemia indistinguishable from that caused by benzol in persons exposed to petroleum benzine, but these are open to the suspicion that the solvent used was not pure benzine, that benzol was present also. Animal experiments for the most part do not reveal marked changes in the blood (Lazarew[180a]). On the other hand Petrini[255a], also on the ground of animal experiments, says that the effect of gasoline fumes on the blood differs from that of benzol only in degree.

Machle[194b], who has had some 2,300 refinery workers under observation for 10 or 12 years, believes that chronic benzine poisoning is very rare. Only among the barrel fillers, who are more heavily exposed, did he find suggestive symptoms, pallor, low red cell count and low hemoglobin, anorexia, nausea, nervousness.

These symptoms were clearly connected with the men's work. The history of exposure is of great importance in making a diagnosis, for no laboratory tests are significant. Moorman[227a] also considers the danger of chronic poisoning slight.

Spencer[300a] in a study of the dispensary attendance of a group of workers exposed to gasoline fumes in cleaning rubber belts found that such exposure increased the numbers seeking dispensary service and reduced the output of the workers. He describes the usual nervous symptoms, also distaste for food, constipation, loss of weight and of strength, pallor, twitching muscles. A change to a good grade of high-boiling kerosene helped decidedly.

Lubricants and cutting oils are mixtures, which usually contain the heavier petroleum distillates, the so-called mineral oils. These are a prolific source of skin lesions from acne to furunculosis. Various causes are given for this action, the plugging of sebaceous ducts by the oil, the presence in the oil mixture of irritating substances such as hydrocarbon sulphonates or unsaturated hydrocarbons, assisted by the overuse of abrasive soaps, which remove the surface cells of the skin and also the natural oils of the skin. Since cutting oil is used over and over again, it gets dirty and may become heavily contaminated with pus-forming bacteria. Staphylococcus aureus has been isolated from such oils and has been known to start an epidemic of skin boils (Shie[287a]).

Finally, brief mention must be made of the fact that certain industrial oils contain carcinogenic substances. The most notorious is the Scottish shale oil, which was discovered to be the cause of scrotal cancer in mule spinners in the textile centers of England. These cases began to appear some years after mineral oil was substituted for animal and vegetable oils. American oils are comparatively free from these substances. Pennsylvania oils seem to be quite free, but mid-Continent oils are not, and cases of epithelioma have occurred in plants where such oils are refined (Heller[135b]).

Part II

TREATMENT AND PREVENTION

By RUTHERFORD T. JOHNSTONE

Foreword

Probably no illness is so needless or so inexcusable as that which arises from occupation. Except for the unforeseen accident such as a sudden, unavoidable escape of gas, for instance, practically all noxious substances can be controlled and the workmen guarded. Typhoid, once a scourge to the civilian population, is now of negligible incidence owing to good hygiene. Just so, many noxious substances of industrial origin, which once caused widespread illness or death, now are well controlled. Industrial management to a great extent has cleaned house and now observes good housekeeping. Maintenance of this desired state is the responsibility of the industrial engineer and hygienist.

It is obvious, then, that the prevention of the occupational diseases should be the goal of industrial medicine. Inability to eradicate completely occupational ill health arises from the constant introduction of new substances with which management and the medical profession are not familiar or the failure of small plants to maintain a program of medical supervision or hygiene. Such being the case, the occupational diseases will continue to occur.

Treatment will be adequate, however, if the physician adheres to the two following precepts:

(1) Determine as quickly and as accurately as possible the occupational cause. In general practice a sore throat may yield to aspirin or a gargle, but such treatment would hardly be sufficient, if it were a case of diphtheria. In industry salve usually is satisfactory for a chemical burn, but inadequate if the burn is due to butadiene. When confronted with an industrial emergency, it is always good practice to get in touch with the responsible man at the plant, where the illness occurred, in order to ascertain the exact nature of the exposure. This simple advice too frequently is neglected.

(2) In only rare instances is the treatment of occupational diseases specific. Rather, treatment is usually a regime directed toward restoration of the function of one or more of the systems of the body. The space allotted does not permit consideration of every noxious substance to which a workman may be exposed, but a few general axioms will serve to guide in the general treatment:

Those portions of the body most likely to be affected by an industrial sub-

stance, especially that large group known as the solvents, are (a) the nervous system, (b) the hemapoietic system, (c) the kidneys and (d) occasionally the liver. There are exceptions to this rule, but they are rare.

An acute exposure to a substance may affect one system of the body, whereas a slow, chronic exposure to that same substance may affect an entirely different system. A further consideration of the selective action of the industrial chemicals introduces these observations:

(1) The disturbance to the central nervous system by the solvents is due largely to the property that resides within them of dissolving fats. Thus, they may act upon the lipoid substance in the nerve fibres or myelin sheaths or upon the cytoplasm. Their anesthetic action also depends on this fat-solvent property, an action similar to that of chloroform, cyclopropane or acetylene. If the exposure exceeds a mild stage, then narcotic effects are produced, even sometimes to the point of sudden death.

(2) Certain solutions or gases manifest a strong affinity for the hemoglobin of the blood or cause alteration or destruction of the blood cells. An exposure to arsine, hydrogen cyanide, carbon monoxide or nitrogen dioxide may be acutely fatal. Slow, prolonged exposure to certain chemicals, such as benzol, may result in anemia of inconstant type.

(3) In excreting certain of the toxic chemicals the kidneys may be damaged. This is quite often a delayed reaction as in carbon tetrachloride poisoning.

(4) Also the liver in metabolizing and detoxifying certain of these noxious substances may be affected by constant, repeated assault. The chief chemical offenders are the chlorinated naphthalenes, carbon tetrachloride, trinitrotoluene, and one or two others.

These foregoing observations rightly belong under the discussion of diagnosis but have been made here to serve as sign posts for treatment.

Sulphur Dioxide

Irritation of Eyes. — Workers in industrial plants, firemen or refrigerator men, who are apt to encounter this gas, should wear gas masks. Treatment of an eye injured by this gas is similar to that of the eye injured by ammonia. Copious laving of the eye with water followed by the introduction of saturated solution of boric acid and by the use of a local anesthetic such as 0.5 per cent. pontocaine hydrochloride is indicated. These are followed by the application of olive oil or some similar oil. Corneal ulceration should be watched for carefully and treated appropriately, if it occurs.

Respiratory Disturbances. — For those overcome by the gas inhalations of from 5 to 7 per cent. carbon dioxide in oxygen are to be used over a long or short

period, depending on the severity of the case and the individual patient's reaction. If pulmonary edema is present, oxygen alone should be used. In very severe cases artificial respiration is to be employed coincidentally with the inhalations. In some cases the use of respiratory and circulatory stimulants such as coramine, metrazol and caffeine sodium benzoate may be of value. A few days of absolute bed rest should be advised for those who have had a fairly severe exposure, and this should be continued until all evidence of respiratory embarrassment ceases. During this period codeine phosphate or sulphate gr. $\frac{1}{2}$ to 1 (30 to 60 mgm.), every four to six hours, will alleviate the cough and may be combined frequently to advantage with a soothing cough syrup mixture. Bland oils should be applied to the exposed membranes. For those who display symptoms of acute asthma the subcutaneous administration of $\frac{1}{2}$ to 1 c.c. of 1:1,000 solution of epinephrine may relieve the symptoms. The use of a nebulizer for inhalation of 1:100 epinephrine might be of value also.

In very severe cases pulmonary edema requiring venesection could conceivably occur, although we have not seen such an instance. In such a case acidosis and intense air hunger may accompany the anoxemia. Treatment of the acidosis, if present, should follow the suggested outline given under Methyl Alcohol. Some authors feel that the severely ill patient should not even be asked to move in bed, since any slight exertion may cause the failure of an overworked and asphyxiated heart.

Chlorine

War Use versus Industrial Use. — The author has had experience with two sources of chlorine gassing, one while in World War I and the other from industry. In the first instance the victims were affected more severely because usually they could not withdraw from the hazard. In industry there occur but few severe exposures. Men are warned of the presence of this gas and immediately withdraw. If severe affection occurs, treatment should be directed to the respiratory tract in order to relieve the irritation and congestion.

Immediate Measures. — The patient severely gassed with chlorine should be removed from the toxic atmosphere promptly, and all constricting clothing about the neck should be loosened. He should be kept quiet in a recumbent position and should be wrapped with warm blankets while hot water bottles are applied. Oxygen should be administered in all cases. It is considered best not to wait for cyanosis to develop, since the administration of oxygen often will prevent cyanosis and relieve the pain of deep inspiratory effort. Venesection of from 400 to 600 c.c. is an extremely valuable measure and should be performed early on all patients who have been exposed to heavy concentrations, but, as already indicated, such exposures in industry will be very rare. The early use of such phlebotomy often

prevents development of edema of the lungs, and if used later, often relieves pulmonary edema and cardiac embarrassment. The early intravenous administration of 10 per cent. dextrose in physiological solution of sodium chloride may be combined with venesection to combat shock and reduce viscosity of the blood. As with phosgene poisoning venesection is contraindicated, if the gray stage of anoxemia with pallor, collapse and rapid, thready pulse has been reached.

Relief of Pain and Excitement. — Morphine sulphate is not to be used, if pulmonary edema and respiratory embarrassment have ensued. Some advise, however, its use for relief of pain and excitement soon after injury. Atropine, epinephrine, digitalis and strychnine are not of much benefit. Caffeine sodium benzoate, gr. $7\frac{1}{2}$ (0.5 gm.) or 1 to 2 c.c. of camphor in oil given intramuscularly sometimes produces beneficial results.

Complications. — If pneumonia is a complication, oxygen therapy is continued. If a specific infection superimposed upon the injured lung is demonstrated, the use of the appropriate therapeutic agents, e.g., sulfanilamide, sulfapyridine, sulfathiazole or serum, are advised.

Olive oil in the eyes may be effective. Codeine phosphate or sulphate, gr. $\frac{1}{2}$ to 1 (30 to 60 mgm.), for cough or spraying of the nose and throat with a soothing solution at times is useful, but for this latter use products containing oil should be avoided because of the danger of developing a lipoid pneumonia. The patient should be reassured regarding any permanent effects to the lungs. A neurosis may be avoided by the initial attitude of the physician and malingering obviated by the emphatic imparting of existing statistics and knowledge regarding these cases.

Fluorine

Combating Calcium Deprivation. — Since the mechanism of fluorine toxicity consists of a calcium deprivation, treatment should be designed primarily to correct this and thus render the fluorine inert. In the acute case of poisoning gastric lavage with lime water or a weak solution of calcium chloride together with from 10 to 20 c.c. of 10 per cent. calcium gluconate intravenously from one to three times a day should be used.

Respiratory and Circulatory Complications. — If cyanosis is present, the administration of oxygen by an intranasal tube or by a tent is indicated, and respiratory stimulants may be needed, such as 1 to 2 c.c. camphor in oil intramuscularly, 7 per cent. carbon dioxide in oxygen as an inhalation, 1.5 c.c. coramine intramuscularly or intravenously, or gr. $1\frac{1}{2}$ to $4\frac{1}{2}$ (0.1 to 0.3 gm.) metrazol intramuscularly or intravenously. The latter two or epinephrine, 1 c.c. of a 1:1,000 solution, intramuscularly are indicated for circulatory failure.

Shock. — The use of 1,000 c.c. of 10 per cent. dextrose in saline given slowly

intravenously will be of value in combating shock, particularly if pulmonary edema is absent. The patient is, of course, kept warm with blankets and hot water bottles.

Sedatives in Complications. — Codeine phosphate or sulphate, gr. ½ to 1 (30 to 60 mgm.), repeated every four to six hours, at times is needed to allay violent coughing. The codeine may be given in any of a number of soothing cough syrups. Dilaudid hydrochloride, gr. 1/32 to 1/16 (2 to 4 mgm.) given hypodermically or by mouth, may help also in this regard, as do morphine sulphate, gr. ⅙ to ¼ (10 to 15 mgm.) or pantopon, gr. ⅙ to ¼ (10 to 15 mgm.). These sedatives and one of the barbiturates may be needed to control convulsive seizures.

Bronchial Asthma. — If symptoms of bronchial asthma appear, the use of one of the following is indicated; ephedrine sulphate, gr. ⅜ (24 mgm.), given every four to six hours, neosynephrin, 0.25 to 0.5 per cent. solution used in a nebulizer, aminophyllin, gr. 1½ (0.1 gm.), every four to six hours, or gr. 7½ (0.5 gm.) in 20 c.c. of distilled water, given intravenously slowly over a five-minute period or epinephrine, ½ to 1 c.c. of 1:1,000 solution hypodermically or as inhalations of a 1:1,000 solution from a nebulizer.

Obstipation and *constipation* may need attention, and if vomiting is severe, the further administration of from 5 to 10 per cent. dextrose in physiological saline solution, 1,000 to 3,000 c.c. daily, is to be used. No established treatment exists for *stiffness of the body* due to bony and ligamentous changes, but it appears that on gradual elimination of the fluorine considerable reduction takes place in osseous overgrowth.

Treatment of Burns. — It is suggested that the burns be treated as described by Jones. The burned area is washed thoroughly with, or immersed in, a warm saturated solution of sodium bicarbonate. Then an ointment prepared by thorough mixing of two parts medical paraffin or glycerin with one part of magnesium oxide is massaged into the burned area, and a dressing of the same ointment is applied; 2 c.c. of sterile 10 per cent. calcium gluconate solution is injected into, and under, all areas showing whitened skin. The magnesium oxide ointment dressing is renewed night and morning for five or six days. After this period boroseptic ointment is an efficient and soothing application, and healing can be completed by dressing with ichthyol ointment. The *eyes,* if involved, should be irrigated for at least an hour with normal saline solution, and then the ointment described above should be applied.

Nitrous Fumes

Correction of Pulmonary Effects. — Oxygen, which has been passed through a bottle containing 2 gm. ammonium carbonate to 1.5 ounces of water, should be

administered to patients in acute cases by means of an intranasal tube. McNally recommends a tube in each nostril. For relief of the pulmonary edema intravenous 50 per cent. dextrose in amounts of from 50 to 100 c.c. up to 200 c.c. daily should be used; salyrgan, 0.5 to 2 c.c. intravenously at intervals of three days is also of much value in treating the pulmonary edema. *Sedation for restlessness* will be needed in many cases.

If *pneumonia* appears as a complication, the use of chemotherapy, i.e., sulfanilamide, sulfapyridine, sulfathiazole or serum, may be instituted, if a predominant organism can be demonstrated in the sputum. In case the carbon dioxide combining power is low, the treatment should be that described for acidosis under Methyl Alcohol.

Chronic Exposure. — Persons affected by chronic exposure may be benefited also by intravenous salyrgan. It is said that these patients often find sleeping in a rocking chair easier than in bed. Frequently they will need acetylsalicylic acid or phenacetin, gr. 10 (0.6 gm.), every four to six hours, for the headache, or if this symptom is more severe, codeine sulphate or phosphate, gr. $\frac{1}{2}$ to 1 (30 to 60 mgm.) every four to six hours. Sedation with drugs such as sodium bromide, gr. 10 to 30 (0.6 to 2 gm.), phenobarbital, gr. $1\frac{1}{2}$ (0.1 gm.) or sodium pentobarbital, gr. $1\frac{1}{2}$ (0.1 gm.), three times a day, is needed at times for restlessness. Constipation may need attention. The mouth washes described under Mercury may be of benefit in ulcers of the mucous membranes. The addition of extra vitamins to the diet should be of value.

Welding

Prophylaxis. — Preventive measures include protection of the eyes from flashes, glare and radiant energy, respirators for protection against inhalation and protective coverings of the exposed parts of the body. Indoor welding should be done where the walls are painted black to reduce the reflection, or booths should be provided. Outdoor welding should be done in portable canvas booths.

The *treatment* of metal fume fever and nitrogen peroxide, lead, carbon monoxide or cadmium poisoning, when they occur as a result of welding, is indicated under those headings.

Electric Ophthalmia. — When this occurs, a superficial injury to the corneal epithelium with exposure of superficial nerve terminals will have occurred. The pain frequently is very severe and may require one of the following for relief; morphine sulphate, gr. $\frac{1}{4}$ (15 mgm.), dilaudid hydrochloride, gr. 1/16 (4 mgm.) or pantopon, gr. $\frac{1}{3}$ (20 mgm.). Both eyes should be bandaged completely, and locally anesthetic ophthalmic ointments, e.g., 2 per cent. holocaine hydrochloride, 2 per cent. butyn or 4 per cent. metycaine, are to be used.

Gases from Carbon Arcs

The chief hazard here, when it does occur, is from the oxides of nitrogen. The prevention and treatment of such poisoning have been discussed under Nitrous Fumes.

Prophylaxis. — The important point here again is prevention. The major portion of such prevention consists of adequate ventilation. It has been suggested that each projector lamp should be connected to a flue in which fumes from arc combustion are exhausted by means of motor driven fans to the out of doors. This fan should turn on automatically as the arc is struck, and the exhaust should run at a minimum of 12 cubic feet a minute with a rate nearer 100 being preferable.

Ammonia

General Measures. — If liquid ammonia is spilled upon the clothing, all clothing should be removed immediately and the body thoroughly drenched with water. The eye injured by ammonia should be washed immediately and copiously with water, and this may be followed by the introduction of a saturated solution of boric acid. If pain is severe, the use of a local anesthetic such as 0.5 per cent. solution of pontocaine hydrochloride is indicated. Thereafter the application of olive oil or some similar oil is desirable. Continuous warm boric compresses to the eyes may be of value. The usual treatment for corneal ulcers should be instituted, if this complication occurs, and an ophthalmologist should be consulted.

Respiratory and Circulatory Measures. — If the concentration of fumes has been severe and respiration affected, inhalations of from 5 to 7 per cent. carbon dioxide in oxygen should be given, and if pulmonary edema ensues, the use of oxygen by means of a tent or intranasal apparatus is advised. The administration of such respiratory and cardiac stimulants as the following may be of value; coramine, 1.5 c.c., metrazol, gr. $1\frac{1}{2}$ to $4\frac{1}{2}$ (0.1 to 0.3 gm.) and caffeine sodium benzoate, gr. $7\frac{1}{2}$ (0.5 gm.). Some of the respiratory and cardiac effects may be reflex in origin from the pulmonary bed, and because of this, the intravenous administration of atropine sulphate, gr. 1/75 to 1/60 (0.9 to 1.0 mgm.) and papaverine hydrochloride, gr. $\frac{1}{2}$ (30 mgm.), might be of value. These should be prepared freshly from the powders just before use.

Mercury

Acute Poisoning. — This is usually the result of intentional or erroneous ingestion of the bichloride of mercury and so will not be seen frequently in industry.

However, as indicated by the cases reported by Williams and Schram[336], severe exposure may result in symptoms primarily involving the gastrointestinal tract.

Gastrointestinal Involvement. — In such cases gastric lavage is indicated at once. A number of chemicals have been used with the wash water to precipitate the mercury and to delay its absorption. The most promising agent so far seems to be sodium formaldehyde sulphoxylate. The chief difficulty is that its effect is not great, if as long as fifteen or thirty minutes elapse before it is given. A freshly prepared solution of 10 per cent. of the sulphoxylate with 5 per cent. of sodium bicarbonate is to be used for the gastric lavage, and about 200 c.c. of the mixture is left in the stomach. An intravenous injection of from 10 to 20 gm. of sulphoxylate in a 10 per cent. solution should be given also over a period of from 20 to 30 minutes.

Its use except in the acute case seen quite early is open to question, since there is some experimental evidence demonstrating that, while sodium formaldehyde sulphoxylate is of value in the prevention of the manifestations of poisoning, it actually may aggravate preëxisting intoxication. Monte and Hull[226] felt that its repeated use was inadvisable and strongly doubted its efficacy in any instance. It is probable that acute mercury poisoning will be seen earlier in industrial than in private practice, and hence the therapy outlined may be of considerable value.

Lavage with three tablespoonfuls of charcoal and 20 gm. of magnesium sulphate to a pint of water has been advised by McNally[213]. One gram of charcoal binds 180 mgm. of bichloride of mercury. Following this lavage two eggs in water and a glass of milk are to be administered. This is followed by another lavage with water, and finally four tablespoonfuls of charcoal are given by mouth, not to be removed. The milk, which is used, should have the cream removed, since fats dissolve mercury salts more quickly and aid in the absorption.

Pain and Prevention of Shock. — In these conditions morphine sulphate, gr. $\frac{1}{4}$ (15 mgm.), every four to six hours, is recommended. For further treatment in shock caffeine sodium benzoate, gr. $7\frac{1}{2}$ (0.5 gm.) or epinephrine, 1 c.c. of 1:1,000 solution, may be given hypodermically, and an intravenous infusion of 10 per cent. dextrose in saline (1,000 c.c.) is indicated.

Subsequent Treatment. — Various therapies have been outlined for the subsequent treatment of the patient. Good results have been claimed for the intravenous use of sodium thiosulphate, gr. 15 (1 gm.) in 10 c.c. water, from one to six times daily, for from three to five days. Hashinger and Simon[129] reported a patient treated chiefly by exsanguination-transfusion with complete recovery. Koranyi[172] reported complete recovery of a patient with beginning oliguria, hematuria and albuminuria by the use of daily venesection (300 c.c.), daily oral administration of 5,000 c.c. Ringer's solution and the intravenous administration of 20 c.c. of a 10 per cent. solution of sodium chloride. Others have advised

multiple transfusions of from 300 to 350 c.c. Cecostomy has been used with good results.

It is very important that the lowered blood chloride level should be treated by intravenous administration of physiological saline, and that acidosis be treated as described under Methyl Alcohol. Sodium citrate or acetate in amounts sufficient to keep the urine alkaline is to be given by mouth.

A regimen consisting of 250 c.c. of the following mixture has been used at hourly intervals: potassium bitartrate, 1 drachm (4 gm.), sugar, 1 drachm (4 gm.), lactose, ½ ounce (15 gm.), lemon juice, 1 ounce (30 c.c.), boiled water, 16 ounces (500 c.c.) along with 250 c.c. of milk. In combination with gastric lavage with 6 quarts of sodium bicarbonate solution and colon irrigation twice daily, daily sweating in a hot pack and continuous rectal irrigation with a solution of potassium acetate, a drachm to the pint, this treatment has given some good results.

For muscular twitchings of uremia, calcium gluconate, 10 c.c. of a 10 per cent. solution intravenously, is of value.

Chronic Poisoning. — No treatment of demonstrated value in chronic poisoning has been reported. Removal from the hazard is, of course, absolutely essential. The use of sodium thiosulphate might be of value, gr. 15 (1 gm.) in 10 c.c. of sterile water intravenously every other day for a short time.

Nervous Disorders. — Most of the treatment in the chronic case is directed toward alleviation of the nervous affections. Since many of these patients have symptoms similar to those seen with chronic encephalitic Parkinsonism, it has been suggested that a trial of drugs used in that disease be made. The older drugs of this group are scopolamine hydrobromide (hyoscine), gr. 1/200 to 1/100 (0.3 to 0.6 mgm.), two or three times a day, or tincture of stramonium, 60 to 90 minims three times daily.

A drug used more recently is amphetamine sulphate or benzedrine sulphate, 20 to 30 mgm. twice daily at 8 A.M. and at noon, in conjunction with a drug of the atropine group or genoscopolamine, in dosage of 0.5 mgm. granules, one three times per day, increasing the dosage after several days to two or three granules three times a day. The latter is said to have far less toxic effects than atropine, hyoscine and stramonium.

Stomatitis. — For this the following mouth washes may be used; tincture of myrrh, 1 part to from 25 to 50 parts of water, potassium permanganate, 1:8,000 or 2 ounces (64 c.c.) of each thymol, hydrogen dioxide and glycerin with saturated solution of potassium chlorate sufficient to make 8 ounces (250 c.c.).

Good oral hygiene is imperative. A diet high in vitamins with the vitamin B complex particularly added should be of value. Diarrhea or constipation, if present, should be controlled.

Prophylaxis. — The prevalence of this disease can be limited by engineering control. Isolating the process under hoods or exhaust ventilation, control of the dust by wet processes, the use of mechanical conveyors and examination of the atmosphere at intervals, all are preventive measures. Jones observed no cases of intoxication among men working in an atmosphere of less than 30 mgm. of manganese per cubic meter of air. He states that this should not be considered a threshold limit and suggests an atmosphere of 50 mgm. per 10 cubic meters as a maximum. Quarterly medical examinations should be routine in any mill or place where manganese compounds are handled in order to detect early signs or symptoms. Mild neurological signs or symptoms such as drowsiness, languor, muscular cramps and twitching, perhaps coupled with an otherwise unaccountable low white cell count, indicate removal of the workman from the hazard. Daily showers following work should be encouraged by installation of shower baths and education of the employee in this regard.

Nothing of real value in the treatment of these patients has been described. For those mildly affected much improvement, perhaps total, will occur on their removal from the exposure. For those severely affected little improvement may be expected.

Vitamin B_1 and Calcium. — Well-rounded, adequate diets should be given these patients, and general tonics may be used. There is some question concerning the use of thiamine hydrochloride, vitamin B_1, since experimentally large doses of vitamin B_1 encourage retention of manganese, and hence B_1 might be contraindicated here. Since low blood calcium levels have been demonstrated by some, oral calcium preparations and milk may well be included in the diet. The patient should be encouraged to drink adequate amounts of fluids and should be given cathartics, if necessary, in order to secure adequate elimination.

Sodium Thiosulphate and Liver Extract. — McNally[213] thought a patient of his showed some improvement while gr. 15 (1 gm.) of sodium thiosulphate in 10 c.c. water was being given intravenously every other day. He cites the feeding by Charles of liver to these patients with what appeared to be improvement in some. When improvement under liver was noted, it was rapid and occurred in the first few days of the therapy. The use of liver extract intramuscularly, then, in dosages of from 15 to 30 units a day for four consecutive days and the repetition of this dose two or three times a week over an indefinite period of time, depending upon the individual patient, has been suggested.

Chromium

Scrubbing Tissue. — If the lesion or lesions, " chrome holes " or ulcers, are small and superficial, the damaged tissue may be scrubbed thoroughly with 5 per cent. sodium hyposulphite, water or normal saline solution. The purpose of this treatment is to dislodge all tissue containing chromium compounds so that additional damage by burrowing will not occur. After this scrubbing, the wound may be treated like any abrasion of similar severity.

Wet Dressings. — If the ulcers already are too deep for such scrubbing, wet dressings of sodium hyposulphite for a period of from three to five days should be applied to aid in the reduction of the chromium compound. Since the chromium in the flesh is not dislodged by sodium hyposulphite, wet dressings of from 5 to 10 per cent. solution of sodium citrate, sodium lactate or potassium and sodium tartrate should be applied to accomplish this. These wet dressings are continued for from three to five days. At times necrotic tissue in the ulcer will require curettage. Suppuration rarely occurs in chrome ulcers, but cleansing with a mild antiseptic agent following use of reducing agents may be used. Treatment appropriate for any ulcer is used following the therapy outlined above.

Frequently it is desirable to remove the worker from his customary duties, at least during the early stages of treatment.

Prophylaxis. — Prophylactic measures should consist of removal of fumes and dust from the atmosphere, cleanliness within the plant and confining the process within enclosures wherever possible. Respirators or gas masks should be worn. Shower baths and change of clothing should follow the day's work, and the installation of shower baths and locker rooms will encourage this procedure. The skin should be protected by suitable clothing, rubber gloves, protective ointments or oils. The nasal mucosa should be sprayed with an oil prior to going to work.

Metal Fume Fever

La Grippe Regimen. — No specific therapy is indicated in these cases. Patients may be treated as though they had la grippe. The administration of acetylsalicylic acid, gr. 10 (0.6 gm.), every four to six hours combined at times with codeine phosphate, gr. $\frac{1}{2}$ to 1 (30 to 60 mgm.), will afford relief. The forcing of fluids, water and fruit juices, the use of hot drinks and rest in bed are of value. These patients will become symptom-free after absence from exposure for a short time, but for their composure the above regimen is prescribed.

Prophylaxis. — The most valuable point, however, is to adopt an adequate medical and engineering program for prevention of the metal fume fever. The toxic fumes should be controlled at their source by having operations, which give

rise to metal fumes, carried on, if possible, in a closed process. Usually it will be more practical to employ exhaust ventilation with hoods over the process producing the fume. The ventilating system should be designed so that a current of clean air is drawn past the operator and away from him toward the work. Masks and respirators may be provided for protection under unusual circumstances.

Magnesium

When compared with other metals, the toxicity of magnesium is low, yet several disturbances to the body may occur from exposure to it. When alloyed with other metals, a rather typical metal fume fever may occur; secondly, peculiar cutaneous lesions may result from implantation under the skin of small particles of magnesium, and finally, severe burns of the body may occur due to the explosibility and inflammability of the dust of magnesium.

The prevention and treatment of the systemic reaction is the same as that indicated under metal fume fever. McCord[210] and his workers found that magnesium in the tissues reacts with the tissue fluids to give rise to the formation of hydrogen. The gas tends to remain localized in discrete nodules and is followed by a necrosis of the tissue simulating fibroblastic proliferation. This accounts for the slow healing of even minor wounds from small particles of magnesium. The treatment of these wounds demands anesthetization of the involved area and then a careful debridement of the tissue to insure complete removal of all particles. Burns from molten magnesium likewise should be debrided and all tissue apt to contain the metal removed. The denuded area should then be dressed with 5 per cent. sulfanilamide ointment.

Arsenic

General Measures. — As with mercury, phenol and other intoxicants the cases of acute poisoning from arsenic will be rare in industry. When they do occur, the symptoms of vomiting, painful diarrhea, nervousness, thirst, cyanosis and circulatory collapse must be treated. Early, abundant, gastric lavage with warm water is indicated. This is followed by the administration of warm milk. Previously lavage of the stomach with colloidal ferric hydroxide suspension, prepared by adding magnesium oxide to tincture of ferric chloride or a solution of ferric sulphate, was advised. This is now considered by most to be almost obsolete, but as McNally[218] points out, it can do no harm and may delay absorption while the stomach is being washed out repeatedly.

Relief of Pain and Diarrhea. — Morphine sulphate, gr. $\frac{1}{4}$ (15 mgm.), every four to six hours, may be needed for relief of the pain and may aid in controlling the diarrhea. Other drugs, which may be used for relief of the diarrhea and

abdominal pain, include bismuth subcarbonate or subnitrate, gr. 15 (1 gm.), every four to six hours, tincture of opium, 10 to 15 drops, every four to six hours, or camphorated tincture of opium, paregoric, two drachms (8 c.c.), every three to four hours. Approximately two hours prior to starting these latter drugs, it is advisable to give a saline cathartic in full dose.

For the diarrhea the drugs mentioned above, e.g., tincture of opium, bismuth subcarbonate or subnitrate or paregoric, may be used. Porter[261] has reported prompt improvement of the diarrhea and neuritis by the use of 2.6 mgm. of thiamine hydrochloride daily, but if this vitamin is used, larger dosages, from 50 to 60 mgm. per day parenterally, are indicated. The use of nicotinic acid, from 100 to 200 mgm. daily, possibly would be of value in treatment of the diarrhea.

Cyanosis, Circulatory Collapse and Shock. — For cyanosis oxygen inhalations are given, and circulatory collapse and shock are treated as described in other sections, e.g., Mercury and Fluorine. The intravenous infusion of 5 to 10 per cent. dextrose in 1,000 c.c. physiological saline is indicated not only for treatment of the shock syndrome but also for the dehydration and chloride loss which may follow prolonged vomiting and diarrhea. The amount of this intravenous therapy needed will be determined by the patient's course.

Sodium Thiosulphate. — The use of sodium thiosulphate intravenously in both the acute and chronic cases is advised. There has been considerable controversy concerning the use of this drug, but clinically it appears to be of value. Ayres and Anderson[8] demonstrated an increase in the excretion of arsenic in the urine following the injection of sodium thiosulphate in 80 per cent. of 49 cases. The amount to be used may vary from gr. 15 (1 gm.) in 10 c.c. of sterile distilled water every four to six hours during the first twenty-four hours of the acute stage to a similar injection two or three times a week over a period of weeks in the chronic case.

Skin Reactions. — The ulcerations, pigmentation and varied forms of a scaling dermatitis which may be present in the chronically exposed usually disappear after removal from exposure. The following prescriptions may be of value for the dermatitis:

Salicylic acid	22½ grains (1.5 gm.)
Sulphur (ppt.)	22½ grains (1.5 gm.)
Lanolin	1½ drachms (6.0 gm.)
Ung. aqua rosae	1 ounce q.s. ad (30.0 gm.)

Salicylic acid	1½ drachms (6.0 gm.)
Menthol	20 minims (1.2 c.c.)
Lard	2 ounces q.s. ad (60.0 gm.)

Fluids should be forced, and some of the drinking water should be normal saline solution. Milk and a high caloric, high vitamin diet are of general value.

Peripheral Neuritis. — Vilter, Aring and Spies[320] report striking improvement in a case of arsenic peripheral neuritis, in which 20 mgm. of synthetic vitamin B_6 in sterile physiological solution of sodium chloride was given twice daily. Improvement was more marked when 50 mgm. of alphatocopherol was given intramuscularly in conjunction with the vitamin B_6; 50 mgm. of thiamine hydrochloride intravenously for three weeks had failed previously to influence the condition. Physiotherapy also may improve the neuritis. Anemia, if present, should be treated by ferrous sulphate, gr. 5 (0.3 gm.), two tablets three times daily.

Arsine Poisoning. — No specific treatment is available for arsine poisoning. Repeated transfusions are of value, and the administration of iron compounds orally is indicated. Oxygen inhalations will be needed in many cases. The remainder of the treatment should consist of an adequate fluid intake supplemented by frequent intravenous infusions of 5 to 10 per cent. dextrose in physiological saline. The administration in the early morning of saturated solutions of magnesium sulphate, $\frac{1}{2}$ to 2 ounces (15 to 60 c.c.), flavored with a small amount of compound tincture of cardamon, may help in encouraging the flow of thick bile plugging the biliary passages; this, however, is doubtful. A similar attempt might be made by introducing from 40 to 50 c.c. of 33 per cent. magnesium sulphate through a duodenal tube. The stimulants frequently mentioned in other sections, e.g., the section describing Mercury, are to be used, when symptoms of circulatory or respiratory failure appear.

Cadmium

Drugs for Respiratory Relief. — The less seriously affected usually experience sensations similar to an upper respiratory infection, and measures commonly used for the latter often afford relief. These include the use of acetylsalicylic acid, gr. 10 (0.6 gm.), every four to six hours, capsules containing acetylsalicylic acid, gr. 5 (0.3 gm.), phenacetin, gr. $2\frac{1}{2}$ (0.15 gm.), and caffeine citrate, gr. $\frac{1}{2}$ (30 mgm.), at three hour intervals or capsules of codeine sulphate, gr. $\frac{1}{4}$ (15 mgm.) and papaverine hydrochloride, gr. $\frac{1}{4}$ (15 mgm.), at from four to six hour periods. A combination of ephedrine sulphate, gr. $\frac{1}{8}$ (8 mgm.) and amytal, gr. $\frac{3}{8}$ (24 mgm.), at from three to four hour intervals, may afford relief in some. Any of numerous cough syrups containing codeine phosphate or sulphate, pantopon or dilaudid hydrochloride in combination with expectorants such as ammonium chloride, may be of value, e.g.:

Codeine sulphate	$7\frac{1}{2}$ grains (0.5 gm.)
Ammonium chloride	4 drachms (16.00 c.c.)
Syrup of citric acid	1 ounce (30.00 c.c.)
Water to make	4 ounces (120.00 c.c.)

Sig.: Teaspoonful every three to four hours

Irrigations and Gargles. — Irrigation of the throat with warm salt and soda solution, a teaspoonful each of sodium chloride and sodium bicarbonate in one pint of water, or warm glucose solution, corn syrup one part and water two parts, every two hours, may be undertaken. If irrigations are not possible, then gargling either with the salt and soda solution, with 1:5,000 potassium permanganate or with five 5 gr. aspirin tablets crushed in a glass of water may be substituted. Neither the use of silver preparations nor the frequent vigorous swabbing of the throat with other preparations is recommended.

Inhalations. — In some instances inhalations of the following might prove soothing:

Menthol Camphor	aa	4 drachms	(15.0 gm.)
Oil of eucalyptus Oil of dwarf pine needles	aa	1 ounce	(30.0 c.c.)

Sig.: One teaspoonful in one pint of water, steamed and inhaled.

Sedation in the form of barbiturates and intranasal drops may be needed, of from 0.25 to 0.5 per cent. neosynephrin or 0.33 per cent. ephedrine in aqueous solution.

Oxygen Therapy. - Whenever a patient appears to be moderately overcome by these fumes, placing him immediately within an oxygen tent is strongly recommended. This should be instituted without waiting for any signs of pneumonia for, as indicated in our fatal case, these may be absent. Furthermore, irrespective of the presence or absence of pneumonia, oxygen therapy affords a relief for the air hunger which exists. If a specific organism is suspected to be present as a secondary invader, appropriate chemotherapy should be introduced.

Prophylaxis. — Those responsible for the health of workmen should recognize the danger of cadmium and adopt adequate means of removing all fumes by exhaust systems. Workmen should wear respirators at all times when in proximity to cadmium fumes.

Zinc

Prophylaxis. — The preventive measures are the same as those to be adopted with a lead hazard or any dust hazard apt to contain lead. Adequate ventilation, avoidance of the deposits of dust and frequent cleaning of all parts of machinery, floors and walls of collected dust are factors in reducing exposure. Men should be selected, who are free from focal infection. Some authors advise periodic changes of work and comparatively short working hours. The inclusion of adequate fat and milk in the diet is thought to prevent to some degree the occurrence of symptoms in those working with zinc.

If a case of chronic zinc poisoning has been established, the patient should be

removed from his hazard at once. Anemia, if present, is treated by ferrous sulphate, gr. 5 (0.3 gm.), two tablets three times a day. In acute intoxication a few days' absence from the work and treatment as described under Metal Fume Fever will suffice.

Zinc Chloride Burns. — Proper treatment of zinc chloride burns consists of the removal of the necrotic slough and of filling the wound with sodium bicarbonate. Compresses of a warm solution of sodium bicarbonate are to be used then. After the lesion has cleaned up to some extent, it is to be dressed with borated petrolatum, painted with merthiolate or covered with metaphen in collodion. Gloves should be worn by workers handling flux containing zinc chloride. When zinc chloride powder is handled, ordinary washing with soap and water will not remove it, as a rule, while a 5 per cent. solution of hydrochloric acid will.

Selenium and Tellurium

Prophylaxis. — The air breathed by workers should be free of these substances or their presence reduced to a minimum. Frequent sampling is necessary to accomplish this. If the substances are subjected to high temperatures, exhaust ventilation should be in operation. The skin should be protected to prevent involvement. Workmen with known respiratory conditions, impaired liver function or arthritic tendencies should be excluded from this hazard.

In chemists synthesizing organoselenium compounds absorption through the skin is prevented by frequent changes to new gloves, protective cream and scrupulous care in handling products. Protective devices such as rubber and synthetic rubber gloves give only temporary protection, since some compounds, e.g., methylbenzoselenazole, readily penetrate them.

Diuretics and Cathartics. — No specific treatment for poisoning with selenium and tellurium is outlined, but if intoxication has occurred, removal from the exposure with possible hospitalization is necessary. The use of diuretics to secure adequate elimination may be indicated, e.g., ammonium chloride, gr. 15 (1 gm.), from four to six times daily, or theophylline, gr. 3 (0.2 gm.), three times daily. In this regard saline cathartics are useful, such as magnesium sulphate, $\frac{1}{2}$ to 1 ounce (15 to 30 gm.), the effervescent preparation of magnesium citrate, 12 ounces, sodium phosphate, 1 drachm (4 gm.), or the effervescent preparation of sodium phosphate, $2\frac{1}{2}$ drachms (10 gm.).

Relief of Symptoms. — Upper respiratory symptoms may be treated as described under Cadmium. Intravenous 50 per cent. dextrose, 50 to 100 c.c., may aid in edema of the lungs, as may salyrgan, $\frac{1}{2}$ to 2 c.c., intravenously at intervals of three or four days. If kidney degeneration is present, the use of salyrgan probably is contraindicated, although some believe that salyrgan may be used

even in the presence of definite kidney pathology. Inhalations of oxygen by intranasal tube or by a tent may be needed, and intravenous infusions of 10 per cent. dextrose in physiological saline (1,000 to 3,000 c.c. daily) may be necessary, if vomiting or diarrhea is present.

Diet. — The use of a high carbohydrate diet with an increased water intake has been suggested as has the use of concentrates of the vitamin B complex. Experimental work on animals indicated the protective action against selenium of a diet high in protein and low in carbohydrate. There was also some evidence that the ratio of selenium to the protein in the diet seems to determine the toxicity of selenium in food, and that the quality of protein, as well as the quantity, was of importance. For example, casein and lactalbumin tend to counteract the toxicity of selenium, while edestin and gelatin are not effective.

The trial of similar diets in selenium poisoning in human beings has not been reported, but the use of diets high in proteins, such as casein, lactalbumin, etc., might well be worth while in treatment of these patients. In addition, when liver damage is present, the use of a high carbohydrate, high protein diet should be followed.

Also experimentally sodium arsenite, five parts arsenic per million of drinking water, completely prevented symptoms of selenium poisoning. Clinical use of this in treatment of selenium poisoning has not been reported.

Vanadium

Symptomatic. — Since but few cases have been reported, and there is no general agreement about the symptoms, treatment should be directed to the individual case of proved exposure. If Symanski[306] is correct, symptomatic treatment would be directed at the conjunctivitis, the nasopharyngitis and the bronchitis. Some of the detailed therapy directed at the upper respiratory symptoms, as described under Cadmium, may be followed.

Prophylaxis. — In mixing rooms respirators or masks should be worn, and suction apparatus should be installed. Rotation of workers should be practiced, so that they would have days or weeks in which they could recuperate from effects of contact with vanadium.

Cyanides

Methylene Blue Treatment. — Hanzlik and Richardson[126] outlined the most effective measures for treatment in cases of acute cyanide poisoning. Fifty c.c. of 1 per cent. methylene blue solution containing 1.8 per cent. sodium sulphate is injected intravenously and is repeated, if necessary, until 200 c.c. are injected.

Frequently consciousness and reflexes are restored before the first 50 c.c. have been completely injected, but if the patient lapses into unconsciousness or manifests respiratory depression, the methylene blue treatment should be resumed. As quickly as possible proceed with gastric lavage using 5 per cent. sodium thiosulphate; this oxidizes any unabsorbed poison. For lavage 3 per cent. hydrogen peroxide or 0.2 per cent. potassium permanganate solution may be used, if sodium thiosulphate is not at hand. Artificial respiration or 5 to 7 per cent. carbon dioxide with oxygen may be needed.

Circulatory and Respiratory Stimulants. — Caffeine sodium benzoate, gr. $7\frac{1}{2}$ (0.5 gm.), coramine, 1.5 c.c. or metrazol, gr. $1\frac{1}{2}$ to $4\frac{1}{2}$ (0.1 to 0.3 gm.), intramuscularly, may be needed for circulatory and respiratory stimulation.

Sodium Nitrite Treatment. — An alternative treatment is as follows. Give at once a slow and careful intravenous injection of 1 per cent. sodium nitrite solution in five divided injections until 50 c.c. have been injected in about one hour. If improvement is manifested, but prognosis still is unfavorable, the injection may be continued cautiously, but it is to be stopped at once in case of sudden collapse. Epinephrine, 1 c.c. of 1:1,000 solution, should be ready at hand to combat nitrite shock, if necessary. Fortify the nitrite treatment at once with the intravenous injection of 20 c.c. of freshly prepared 5 per cent. aqueous solution of sodium thiosulphate, filtered and, if necessary, continue the injection up to a total of 500 c.c. Treatment directed at further circulatory and respiratory stimulation is to be used as already indicated. The solutions used in these treatments can be sterilized readily by boiling for fifteen minutes. The methylene blue should not be dissolved in physiological solution of sodium chloride, since precipitation occurs.

Both the methylene blue and the sodium nitrite appear to act by producing methemoglobin, which in turn combines with the cyanides to decrease the poisonous effects of the latter. Actually, sodium nitrite forms more methemoglobin, but this probably does not contribute to the physiological recovery from poisoning, and there is danger of sustained circulatory collapse to add to the already precarious state of the patient.

Sodium Nitrite and Sodium Thiosulphate Treatment. — Ingegno and Franco[149] treated two patients with 0.3 gm. sodium nitrite in 10 c.c. water given intravenously at the rate of 2.5 to 5 c.c. per minute and followed this by 25 to 50 c.c. of a 50 per cent. solution of sodium thiosulphate given through the same needle and at the same rate. They warned that the sodium nitrite and thiosulphate must not be mixed before administration. If signs reappeared or persisted, one-half the dose of each antidote was repeated one hour later. They used also amyl nitrite inhalations for from fifteen to thirty seconds every two or three minutes.

Diet. — A high fat diet has been shown experimentally to reduce the mortality from sodium cyanide poisoning. In the rare case of chronic cyanide poisoning such a diet possibly would be of use in addition to symptomatic treatment. The use of sodium thiosulphate, 10 c.c. of a 10 per cent. solution intravenously, two or three times per week might be of value. Removal at once from exposure is, of course, necessary.

Carbon Tetrachloride

The severe case of carbon tetrachloride poisoning will require a rigid régime, the purpose of which is twofold, to treat the liver and renal damage and to restore a normal blood chemistry. The patient should be removed from all contact with the substance. He should be supplied with an abundance of fresh air and with inhalations of from 5 to 7 per cent. carbon dioxide in oxygen, if necessary, for respiratory stimulation.

Increasing Blood Calcium Level. — These patients have a low blood calcium level. Therefore, a high calcium intake should be provided to bring their blood calcium to a high or normal level, which it has been shown experimentally will prevent liver and renal damage to some degree. This can be accomplished by giving 10 c.c. of a 10 per cent. solution of calcium gluconate intravenously two or three times daily with 12 gm. calcium gluconate or 8 gm. of calcium lactose by mouth.

Proteins in Diet. — The diet itself should contain a high proportion of carbohydrates, 200 to 250 gm. or more per day, together with a low fat and a low meat protein ratio. The meat protein is limited because of the evidence that increased retention of guanidine prolongs and increases the symptoms of carbon tetrachloride poisoning. However, in view of the demonstrated value of protein in liver regeneration, a high level of other forms of protein should be maintained. Actually, following the early acute symptoms a still higher protein level probably would be of value. Bread, milk, sugar and karo syrup are obviously of much value in the diet, to which may be added also extra vitamins.

Dextrose Solutions. — The intravenous administration of from 2,000 to 3,000 c.c. daily of 10 per cent. dextrose in physiological saline is indicated. In renal disease or when circulatory collapse induces defective renal function, the injection of physiological solution of sodium chloride occasionally may produce or aggravate acidosis. This effect is brought about chiefly by diluting the bicarbonate already in the body at a time when the kidneys are not excreting the excess of chloride. In some instances, then, the use of 10 per cent. dextrose in distilled water rather than in 0.9 per cent. sodium chloride solution may be indicated. However, in most instances the 0.9 per cent. sodium chloride solution

may be used, since even abnormal kidneys excrete salt solution well, if serum proteins are not reduced, or if cardiac failure is not present. Dextrose solutions by providing food and aiding the circulation help the kidneys to adjust extracellular volume and concentration, when sufficient sodium chloride is available.

The administration of from 50 to 200 c.c. of 50 per cent. dextrose intravenously per day is of value also, but when cardiac involvement is present, not more than 50 c.c. should be given at one time. It has been suggested that some of the fluids may be given per rectum rather than intravenously; 120 c.c. of 10 per cent. dextrose every four hours may be used rectally.

Insulin. — From 5 to 10 units of insulin three times per day may aid in the oxidation of the intermediate products of protein, fat and carbohydrate. There have been a few reports of the satisfactory use of Hartmann's buffer solution and of methylene blue, but neither of these agents has been used extensively in these cases.

Digitalis. — This has been advised routinely for the treatment of myocardial involvement but would seem to be of questionable value in most cases. When used, regular digitalizing doses of gr. $1\frac{1}{2}$ (0.1 gm.) should be employed. Epinephrine should not be used, particularly if myocardial involvement is present.

Diuretics. — Diuretics other than the mercurial ones are indicated. In treating oliguria or anuria the use of papaverine hydrochloride or sulphate, gr. $\frac{1}{2}$ (30 mgm.) intravenously or by mouth, is said to be of value on the basis that these drugs relax the arteriolar spasm associated with the toxic nephritis. There are claims of success for the use of hexylresorcinol for treatment of kidney irritations.

Other Medication. — Free catharsis is of value, but oily preparations are contraindicated. Transfusions of blood sometimes are necessary. If anemia of the secondary type is present, ferrous sulphate in enteric coated tablets, gr. 5 (0.3 gm.), two tablets three times per day, should be prescribed, and if a macrocytic type of anemia accompanies the liver damage, the use of liver extract is indicated. If any bronchial conditions develop, inhalations of compound tincture of benzoin and pine-needle oil followed by a cough syrup containing codeine phosphate or sulphate should be used. Sedation may be necessary for the restless or for the excited. When the eyes are involved, their treatment should be consigned to the ophthalmologist.

Experimental work with a purified concentrated hog's liver extract has demonstrated an accelerated healing of liver tissue in rats after carbon tetrachloride poisoning in addition to protection of the liver from damage. The active ingredient appeared to be sodium xanthine. Its clinical use in carbon tetrachloride poisoning has not been reported so far.

Prophylaxis. — From the standpoint of prophylaxis proper ventilation is essential. In addition closed systems should be used, or if these are not possible,

positive pressure helmets may be necessary, when the concentrations are very high. Exhaust systems should be provided with intakes at the floor level rather than near the ceiling. The possibility of skin contact with the substance should be eliminated. There should be frequent examination of workers and careful selection of those who are to work with this hazard. Rotation of workers should be frequent. The diet of carbon tetrachloride workers should be high in calcium including at least one quart of milk daily. Alcoholic beverages should be avoided.

Trichlorethylene

Prophylaxis. — From the standpoint of prophylaxis several points are important. Addiction to this solvent has been reported by numerous investigators, and it is known that men at times will inhale it voluntarily. For this reason rotation of men should be practiced where this substance is used for long periods. In degreasing plants, where heat is used, acid-proof flues are necessary to carry off the fumes to the outside. If such flues are not provided, the gas heating process should be condemned. In the general use of trichlorethylene proper ventilation should be enforced strictly at all times, and the skin should be protected by clothing and gloves as nearly as possible. It is well to apply ointments of oil or fat, for example a mixture of equal parts of vaseline and rose water ointment, to areas such as the hands and arms, which are liable to be most exposed.

Dermatitis. — For patients, who present a dry, fissured type of dermatitis, the chief therapy is similar to that suggested in those measures to be used in prophylaxis. The patient should be removed from exposure to the offending solvent until the dermatitis has cleared, and in quite a few cases it will be best to advise him to change his occupation, although careful protection of exposed parts of the body may prevent recurrence of the dermatitis. For the treatment of the acute dermatitis simple ointments, such as rose water with 1 per cent. phenol and 0.5 per cent. menthol, may be of value.

The Acutely Ill Patient. Respiratory Stimulants. — These are needed. Here the most valuable of all will be inhalations of a mixture of from 5 to 7 per cent. carbon dioxide with oxygen. When such inhalations are not available, artificial respiration by the Schaefer method must be used, and later, if pulmonary edema is present, the administration of oxygen either by a tent or intranasal apparatus will be of value. It should be remembered, however, that oxygen in itself is not a respiratory stimulant, and when used without the addition of carbon dioxide, actually may depress rather than stimulate respiration. The intravenous or intramuscular injection of coramine, 1.5 c.c. or the intramuscular injection of metrazol, gr. 1½ to 4½ (0.1 to 0.3 gm.), are of questionable value in treatment of the respiratory failure, although their use has been advised.

Shock. — They may, however, be of definite value if shock is present. For treatment of this from 1 to 2 c.c. of camphor in sterile oil or of caffeine sodium benzoate, gr. $7\frac{1}{2}$ (0.5 gm.), may be used. Of much greater value will be the use of transfusions of citrated blood and the intravenous infusion of 1,000 c.c. of 10 per cent. dextrose in normal saline solution.

Diet. — Following the very acute period soft diet and normal fluid intake may be resumed, but if symptoms of nausea and vomiting persist, the use of from 2,000 to 3,000 c.c. daily of 10 per cent. dextrose in physiological saline is advisable. The administration of thiamine chloride, vitamin B_1, in dosages of from 30 to 60 mgm. daily, at first parenterally, has been suggested in treatment of the neurological manifestations. During the convalescence a high caloric diet with vitamin adjuncts should be given.

Exposure to Phosgene. — If the acutely ill patient has been exposed to phosgene resulting from the decomposition of trichlorethylene by gas flames, he may present a somewhat different picture, with pulmonary edema, dyspnea and cyanosis playing prominent parts in the picture. Here again respiratory and circulatory stimulants are indicated. In addition venesection of 500 c.c. may be of value in treating the pulmonary edema. During World War I intratracheal medication of from 1 to 3 drachms of the following mixture two or three times per day was found to be beneficial after the very acute stages had passed: 5 per cent. each of guaiacol, camphor and menthol in liquid petrolatum or olive oil. No instances of lipoid pneumonia from the use of this preparation are mentioned.

The Gray Stage. — During the acute phase a syndrome may occur, referred to in the findings of the chemical warfare service as the gray stage, in which pronounced pulmonary edema, almost utter inability to breathe and shock are seen. In such a stage the temperature falls, and there is a marked increase in blood concentration necessitating oral and intravenous administration of physiological saline solution. A fine degree of medical judgment is needed to balance the need for venesection on the one hand and for decrease in excessive blood concentration by administration of fluids on the other.

Tetrachlorethane

The chief concern in formulating a therapeutic regimen is directed toward the improvement of liver function.

Diet. — The patient should be given a diet high in carbohydrate, since this food factor aids in the regenerative process of the injured parenchymatous liver cells. In addition the inclusion in the diet of foods high in protein is indicated, since recent research indicates a protective action to the liver by diets high in protein. The ability of the liver to deaminize and metabolize amino acids appears

to be normal up to the very last stages of hepatic insufficiency. The fat content of the diet should be low; from 200 to 250 gm. of carbohydrate and from 1.5 to 2 gm. of protein per kilogram of body weight thus should be included in the diet.

Infusions of Dextrose. — It is of particular importance, when severe or even moderate liver damage is present, to administer by intravenous infusion from 5 to 10 per cent. dextrose in physiological saline solution or in distilled water, preferably about 3,000 c.c. daily. It may be necessary in very acute cases to give such infusions by continuous intravenous drip.

Vitamin K and Bile Salts. — The use of 2-methyl-1, 4-naphtho-quinone, synthetic vitamin K, and of bile salts has been suggested. Vitamin K may be given orally or parenterally in doses of from 1 to 4 mgm. daily, and the bile salts may be administered orally in dosages of from 2 to 3 mgm. of desiccated whole fresh bile. Prior to the administration of these substances the prothrombin level of the blood should be determined, and a subsequent check on this reading will indicate whether the vitamin K is of value in the individual case.

On the question of the value of vitamin K in such cases there is considerable disagreement. There is evidence to indicate that, if hepatic injury is severe enough, vitamin K is not effective in correcting the prothrombin deficiency. Since, however, little toxic reaction to vitamin K or to whole fresh bile occurs, their trial use is suggested. In cases of hemorrhage blood transfusion is indicated, and for secondary anemia, if present, enteric coated tablets of ferrous sulphate, gr. 5 (0.3 gm.), two tablets three times daily, should be used. The intravenous administration of 10 c.c. of a 10 per cent. solution of calcium gluconate twice daily will be of value. The oral use of 12 gm. calcium gluconate or 8 gm. calcium lactate will supply about 1 gm. of calcium daily. Under normal conditions the daily calcium requirement is from 0.5 to 1 gm.

Methyl Chloride

Inhalations and Artificial Respiration. — Severely exposed workmen should be removed at once from contact with the substance. Inhalations of from 5 to 7 per cent. carbon dioxide in oxygen certainly are indicated, and artificial respiration may be needed. In this phase of the treatment the object is to remove from the lungs all possible methyl chloride. It is felt by some that these inhalations should be continued every three hours over the first twenty-four to forty-eight hours. The respiratory and cardiac stimulants frequently mentioned in other sections, e.g., the section on Phenol, should be used when respiratory or circulatory failure appears.

Treatment as in Methyl Alcohol Poisoning. — The methyl chloride taken into the body is decomposed into methyl alcohol and hydrochloric acid. The latter

forms relatively innocuous substances such as potassium and sodium chlorides in the blood. The treatment for the methyl chloride poisoning, then, becomes the same as for methyl alcohol poisoning. The patient is hospitalized immediately, and energetic treatment of his acidosis is begun. For details of this section on Methyl Alcohol should be consulted.

Convulsions and Restlessness. — If convulsions occur, they require 1 drachm (4 gm.) of potassium bromide in 4 ounces (120 c.c.) of water as a retention enema, but under no conditions should chloral or chloroform be given. For the convulsions and restlessness the use of other sedatives such as phenobarbital, seconal, nembutal, sodium amytal and sodium luminal as well as others of this type may be of value.

Abdominal Pain. — Some cases, in which paroxysms of severe abdominal pain have been a prominent part of the picture, are reported. In these morphine sulphate, gr. $\frac{1}{4}$ (15 mgm.), has been used together with intravenous calcium. It would appear of value in cases presenting such severe cramps to use 10 c.c. of 10 per cent. calcium gluconate intravenously, repeated as needed. The use of 1 c.c. of 1:2,000 prostigmine methylsulphate with the morphine may enhance its effectiveness and allow reduction of the amount of morphine.

Anemia. — If this develops, it is to be treated with ferrous sulphate, gr. 5 (0.3 gm.), two or three times a day, if it is of a secondary type; if it appears to be of a macrocytic type, it is to be treated with liver-extract preparations.

Ethylene Dichloride

Treatment should consist of general supportive measures as indicated with the other solvents and of similar prophylaxis. The use of a high carbohydrate, high calcium diet has been of definite value. The intravenous administration of 10 c.c. of 10 per cent. calcium gluconate to the patient shortly after his admission to the hospital has relieved markedly the epigastric cramps and vomiting. This presumably is because of the relaxing effect on smooth muscle of the calcium gluconate. As in treatment for the other solvents it will be valuable to use intravenous infusions of from 5 to 10 per cent. dextrose in physiological solution of saline, if chloride loss following vomiting is present, or in distilled water, if it is felt that the salt content will increase renal damage, in amounts varying from 2,000 to 3,000 c.c.

Chlorinated Naphthalenes and Diphenyls

Prophylaxis. — It should be reiterated constantly that the primary treatment is prevention. Ventilation should be proper. The recommendations of Green-

burg[99] and his associates concerning the type of person to be employed, where this hazard exists, should be followed. The knowledge of an existing hazard by both the employer and the employee and the recognition of certain early symptoms by the workman will greatly reduce actual intoxication. Obviously this is an educational program.

No specific therapy has been evolved for these cases. The acneform skin lesions and the liver damage are the two symptoms toward which treatment is to be directed chiefly.

Skin Lesions. — Prevention of the papulopustular skin eruption frequently may be accomplished by installation of showers and by the formulating of rules requiring a change from street clothing to work clothing at beginning of the day's work and, following a shower, a change back to street clothing at the end of the work period. The most satisfactory treatment of the skin eruption, once it has occurred, consists of quartz light and x-ray therapy together with mechanical removal of the comedones. The worst cases are to be treated with quartz light each day for from 15 to 20 minutes, the less serious ones three times per week, and the mild ones once per week. The pustules should be opened, and these might respond well to the use of sulfathiazole powder or ointment locally. Extreme body cleanliness should be practiced. Cases of very resistant exfoliative dermatitis have been described, in which the use of sodium thiosulphate, splenic extract, calcium gluconate, autohemotherapy, roentgen therapy and numerous baths, powder and ointments were of little avail.

Liver Disorder. — This may be treated much as described under Tetrachlorethane, the chief points being a high carbohydrate, high protein diet with adequate fluid intake and particularly, intravenous infusions of 5 to 10 per cent. glucose in normal saline solution in amounts of from 2,000 to 3,000 c.c. or more daily. The use of calcium and of sodium xanthine experimentally has been of no value in prevention or treatment of the liver damage due to the chloronaphthalenes. This differs, for example, from the treatment of carbon tetrachloride poisoning in which calcium products are of much value.

Alcohols: Glycols: Alcohol-Ethers

All alcohols have a narcotic effect, which is progressively greater with increase in molecular weight. The higher alcohols, like butyl and amyl alcohol, have in addition an irritant action as well as some poisonous action on the protoplasm. Whenever any of these are used industrially, adequate ventilation is essential for protection of the workers.

Special Measures in Industrial Cases. — The treatment of the case of methyl alcohol poisoning seen in industry will differ to some extent from that seen in

private practice. In industry the toxic action usually will have been produced by absorption through the skin or by inhalation in contradistinction to the ingestion of the product more commonly seen in private practice. For this reason the use of emetics is not indicated, and the value of gastric lavage with 4 per cent. solutions of sodium bicarbonate will not be so great, although this latter procedure may be used and will, at least, be of value in treating the resulting acidosis.

Correction of Acidosis. — The most important phase of the treatment is directed at correcting the acidosis, which is produced in the body by the formation of formic acid from the methyl alcohol. It has been the writer's experience to find that medical literature frequently advises treatment of acidosis but fails to give details of such treatment. For this reason some detail in the treatment of acidosis is included here. In other sections, where treatment of acidosis is suggested, reference to this description has been made. The use of sodium bicarbonate or sodium lactate intravenously is advisable. It is safest to calculate the dose necessary to restore the serum bicarbonate according to the method of Hartmann and Senn[128]:

$$\text{mM.} = \frac{(60\text{-}CO_2)0.7W}{2.24}$$

mM. = millimols of sodium bicarbonate or sodium lactate
CO_2 = serum carbon dioxide content in volumes per 100 c.c.
W = body weight in kilograms

One mM. of sodium bicarbonate is 0.084 gm.; 1 mM. of sodium lactate is contained in 1 c.c. of 5-molar sodium lactate. In marked acidosis, when serum carbon dioxide is not known, 5 mM. of sodium bicarbonate (1.4 gm.) per kilogram of body weight is a safe dose. Hartmann and Senn[128] recommend the injection of one-half the calculated dose of sodium lactate intravenously and one-half subcutaneously as one-sixth molar sodium lactate. R-molar sodium lactate is obtainable in sterilized ampules, which most physicians will find more convenient than sodium bicarbonate. Sodium bicarbonate cannot be boiled or autoclaved in an unsealed vessel without forming the highly toxic sodium carbonate. Sodium bicarbonate may be weighed and added with aseptic precautions to sterile water or dextrose solution and injected intravenously as a 2 to 5 per cent. solution. Both sodium bicarbonate and sodium lactate may be given by mouth, when the patient is able to take them by this route.

Solutions for Use in Acidosis. — Several very valuable solutions for use in treatment of acidosis are on the market. A solution containing sodium chloride, 6.5 gm., sodium bicarbonate, 2.5 gm. and potassium chloride, 0.18 gm. per liter, may be prepared by the addition of the contents of a 50 c.c. ampule of this preparation to 500 c.c. of sterile water. It may be used in practically all cases of acidosis with-

out additional sodium bicarbonate and may be given subcutaneously or intravenously. Lactate-Ringer's solution, sodium chloride, 6 gm., sodium lactate, 2.7 gm., potassium chloride, 0.4 gm. and calcium chloride, 0.2 gm. per liter, is equally valuable and is available in concentrated form in ampules the contents of which are to be diluted with distilled water.

Other Measures. — In addition to treatment of the acidosis the patient should be kept warm. Intravenous infusion of 10 per cent. dextrose in physiological saline may be of value in supporting him, and for this there has been advised also the intramuscular administration of atropine sulphate, gr. 1/40 (1½ mgm.), not to be repeated, strychnine sulphate, gr. 1/30 (2 mgm.), metrazol, gr. 1½ (0.1 gm.), camphor in oil, 1 to 2 c.c., coramine, 1.5 c.c., or caffeine sodium benzoate, gr. 7½ (0.5 gm.). Aromatic spirits of ammonia, ½ to 1 drachm (2 to 4 c.c.), by mouth is said to be of value. If pain is present, the use of morphine sulphate, gr. ¼ (15 mgm.), despite its central depressant effect, or codeine phosphate, gr. 1 (60 mgm.), is used frequently, and if delirium is present, scopolamine hydrobromide, gr. 1/300 to 1/200 (0.2 to 0.3 mgm.), may be combined with the morphine.

Use of 50 per cent. solutions of sucrose in treatment of cerebral edema, if present, has been suggested. The oral administration of a large dose of magnesium sulphate usually is part of the routine. With the exception of the eye most abnormalities from chronic exposure clear up after removal of the exposure.

Benzene (Benzol) and Its Homologues

What is said here of treatment for benzene may be applied to toluene, xylene and a few of the less toxic homologues of benzene.

Prophylaxis. Frequent Physical and Laboratory Examinations. — Constant vigilance by blood examinations and air analysis should be the established order wherever benzene constitutes a hazard. The routine white cell count commonly resorted to should be supplanted by a complete blood study for reasons emphasized in earlier paragraphs of this chapter. Only those in fine physical condition should be placed where a benzene hazard may arise, and frequently physical as well as laboratory examinations are indicated.

Men should be rotated, and when the least variation from the normal is noted, the worker should be removed from his exposure. Likewise workers should be instructed to report for examination upon noting bleeding from the nose or gums or other mucous membranes, or when unaccountable subcutaneous hemorrhages or discolorations are noted. Safety engineers have done an excellent job of preventing accidents by educating the employees regarding the dangers, which exist in certain types of employment. It is high time for a similar educational campaign to be conducted in the various occupational diseases. Many serious cases

of poisoning from benzene and other noxious agents could be prevented, if the employees themselves knew, or were informed of, certain early signs or symptoms. To find a case of far advanced anemia in one, who for some time had noted bleeding and other symptoms of general malaise without reporting these, denotes not only ignorance on his or her part but a failure in education or instruction.

Proper Ventilation. — Obviously proper ventilation is extremely important. Since benzene fumes tend to form pockets and are very diffusible and heavier than air, the ventilation should be general and from the floor by means of suction.

Dermatitis. — Dermatitis is prevented by the rubbing into the skin of olive oil or other animal or vegetable fat or by the use of a wax ointment before handling the substance. Rubber gloves may be used, but ordinarily they do not withstand the action of benzene, so synthetic rubber, which resists the solvent action much better, should be substituted.

Anemia. Blood Transfusions. — In those workers, who have developed anemias of varying degrees together with other symptoms of benzene poisoning, the most valuable form of therapy is blood transfusion repeated frequently, if necessary. In attempting to carry out this type of therapy, Gray, Greenfield and Lederer[97] were confronted with a case of autohemagglutination, although the patient had had three previous transfusions. They point out that autohemagglutination is the interaction of the agglutinin of the serum with the agglutinogen of the red blood cell and can occur only at a temperature below that of the body. They eliminated the difficulty by heating the serum and cells to body temperature.

Liver Extract and Iron. — Since the anemia frequently is of the macrocytic, hyperchromic type, liver extract intramuscularly in large dosages, 15 to 30 units daily for four days, then every two or three days, or ventriculin orally, 15 to 30 gm. daily, sometimes both, should be tried. If the anemia appears to be of a secondary type, the use of iron in the form of ferrous sulphate, gr. 5 (0.31 gm.), two or three times a day, is advised. Leucopenia indicates the trial of pentnucleotides intramuscularly, 10 to 40 c.c. daily, although marked improvement under this form of therapy usually has not been demonstrated in these cases.

Roentgen Rays. — For further stimulation of the blood forming organs, the use of roentgen therapy to the long bones and spleen and bone marrow extracts has been suggested. Others have used ascorbic acid in moderately large doses with reported success.

Diet. — The diet should contain nourishing food with an excess of animal fats and a high calcium content. Calcium preparations may be given orally as supplements to the diet. Intravenous infusions of from 1,000 to 3,000 c.c. daily of from 5 to 10 per cent. glucose in saline are of value. Good results from the use of ascorbic acid in daily doses of from 200 to 400 mgm. intravenously and orally, until a normal vitamin C level is attained, have been claimed.

Mouth, Nose, Throat and Skin Hygiene. — Because these patients frequently die of a terminal infection, particular attention should be paid to mouth, nose, throat and skin hygiene.

Phenol

Principal Steps. — The case of phenol poisoning encountered in industry usually will differ from that seen in private practice in that the mode of poisoning will be by absorption through the skin or by inhalation in the form of vapor rather than by drinking of the material. The most important steps, then, in the acute case of industrial phenol poisoning will be; (1) the removal of all clothing to prevent further absorption, (2) washing of all involved areas on the skin with a 25 per cent. solution of either alcohol or glycerin and (3) treatment of shock.

Respiratory and Circulatory Measures. — The patient should be kept as warm as possible, and symptoms of circulatory shock and respiratory depression should be treated by use of the various stimulants mentioned in previous sections. For respiratory stimulation the most valuable are inhalations of oxygen with from 5 to 7 per cent. carbon dioxide and solutions such as metrazol, gr. $1\frac{1}{2}$ (0.1 gm.), camphor in oil, 1 to 2 c.c., caffeine sodium benzoate, gr. $7\frac{1}{2}$ (0.5 gm.), intramuscularly or coramine, 1.5 c.c., intravenously or intramuscularly. For the circulatory shock intravenous infusion of 1,000 c.c. of 10 per cent. glucose in distilled water and drugs such as the coramine, caffeine or epinephrine hydrochloride, $\frac{1}{2}$ to 1 c.c. of 1:1,000 solution intramuscularly, may be used. However, there is some question concerning the advisability of the use of epinephrine in cases of poisoning. The use of digitalis preparations is mentioned frequently in treatment of circulatory shock but seems of very questionable value in this situation.

First-aid Measures. — As first-aid measures a quantity of olive oil, cod-liver oil, cottonseed oil, castor oil or any other available vegetable oil should be given by mouth as well as egg-white. Mineral oil affords no protection against phenol, since the solubility of phenol in it is quite small, about 1 in 50 parts. Alcohol, previously thought to be of value, should not be given by mouth or used for gastric lavage, since alcohol, although a good solvent for phenol, seems to increase the rate of absorption of phenol from the stomach. Thorough gastric lavage with 10 per cent. solution of glycerin or, if this is not available, with sodium sulphate, 15 gm. (4 drachms) to the pint of water, should be carried out.

Nephritis, if it occurs as a complication, should be treated by the standard methods employed for this disease.

It has been shown recently by Meyer[218] that a high protein diet given to rats increased very definitely their resistance to phenol poisoning. This observation, however, probably has no great practical significance in treatment of the poisoning, once it has occurred, other than to suggest the use of a high protein diet.

Nitrobenzene

Immediate Measures. — In acute poisoning the contaminated clothing should be removed at once, and areas of the skin, on which the substance has been spilled, should be cleansed with alcohol. Gastric lavage with water containing epsom salt, which delays absorption, is performed, although as in phenol, mercury and arsenic poisoning the lavage is not of as much value in the industrial case as in that of poisoning by ingestion, which is more apt to be seen in private practice. Oils, milk and alcohol should not be given by mouth, since they tend to favor absorption.

Prevention of Respiratory and Circulatory Failure. — Inhalations of carbon dioxide, 5 to 7 per cent., in oxygen are indicated for respiratory stimulation and coramine, 1.5 c.c., metrazol, gr. $1\frac{1}{2}$ to $4\frac{1}{2}$ (0.1 to 0.3 gm.), caffeine sodium benzoate, gr. $7\frac{1}{2}$ (0.5 gm.), or camphor in oil, 1 to 2 c.c., may be given intramuscularly for respiratory and circulatory stimulation. Intravenous infusions of from 5 to 10 per cent. glucose in physiological saline solution are indicated, and transfusion of blood, 350 to 500 c.c., may be necessary. If acidosis is present, it should be treated as described under Methyl Alcohol. Epsom salts, $\frac{1}{2}$ to 1 ounce (15 to 30 gm.), usually is to be given orally.

Hepatic Injury. — Following the acute stage, treatment directed at correction of the liver damage may be necessary, and this should follow pretty closely that outlined under Tetrachlorethane. If a macrocytic type of anemia develops, liver extract, 15 to 30 units per day for the first three or four days and then at intervals of from 5 to 10 days, should be given.

Carbon Disulphide

Prophylaxis. — The most important point is prevention of such poisoning. Preventive measures consist primarily of rigid examination of the plants to insure modern, safe equipment and the presence of adequate ventilation. The storage and pipe conveyance of carbon disulphide must be satisfactory, and explosions should be guarded against. Medical examination of those exposed to this hazard should be at intervals not greater than one month. Men should be taught to report the first intimation of any unusual symptoms, and if this solvent is the suspected cause of the complaints, the employee should be removed at once from the hazard. The drinking of alcoholic beverages by those apt to be exposed to carbon disulphide should be discouraged.

Diet. — To date no adequate or specific treatment for cases of chronic carbon disulphide poisoning is known. It would seem likely in view of the similarity of many of these cases to Korsakoff's syndrome that a diet high in vitamin content with the vitamin B complex as an adjunct would be of value. If vitamin B com-

plex is to be used, the dosages should be relatively large, e.g., from 50 to 60 mgm. of thiamine chloride parenterally daily, 200 mgm. of nicotinic acid daily, 1 mgm. of riboflavin three times per day, 20 mgm. vitamin B_{12} twice daily parenterally and so on. Liver extract in dosages similar to those advised in the chapter on Manganese might be tried.

Psychiatric and Ophthalmological Attention. — The aid of a psychiatrist will be needed for most of these patients, since a program of mental hygiene will need to be instituted. The ophthalmologist should be consulted on problems relating to the eyes.

Exercises for existing muscular weakness, sedation and tonics may be of value. If Parkinsonian-like symptoms are present, a trial of those drugs mentioned in the section on Mercury for control of these manifestations might be made.

The acute case will be seen rarely. When such a case does occur, artificial respiration, 5 to 7 per cent. carbon dioxide in oxygen inhalations and the respiratory and circulatory stimulants mentioned in the sections on Trichlorethylene and Alcohols are to be used.

Butadiene

In the manufacture of synthetic rubber the workers are exposed to butadiene gas among other substances. No internal disturbance of any type has been noted by the writer, but burns of the skin are fairly common. It is significant that frequently the exposed individual is unaware that his skin has been burned for several hours following contact.

As soon as the worker is aware of, or even suspects, an exposure, he should have all clothing removed and then should be placed in a shower bath for a thorough and prolonged washing of the entire body. This is to be followed by a general application of calamine lotion and then fresh clothing worn.

Radium

Radium poisoning need never occur, if proper precautions are taken, but these precautions must be carried out meticulously, since radium enters the body with considerable ease. Necrosis of the bones, anemia and buccal lesions were noted in dial workers in the 1924–1925 outbreak of this disease. It was felt at that time that the radium entered the body through ingestion, since these workers were accustomed to " point " their brushes with their mouths. Today radium workers are cognizant of this danger and avoid acts which might lead to ingestion of this substance. Prevention is directed today against the inhalation of the dust, which primarily imposes the obligation of correct hygiene upon plant management.

In general there are two groups of workers in radium dial manufacture who

must be protected. The first of these are the painters, usually young women. These should be provided with individual glass hoods within which the operation is performed. The glass protects the worker's face, especially the breathing zone, yet enables a clear vision of the working field. The booth should be exhausted by suction ventilation. The head should be covered, the clothing simple and no personal articles, such as cosmetics, cigarettes, candy or food, permitted within the radium room.

Rigid personal hygiene must be enforced under supervision and not left to the individual's inclination. An excellent régime has been suggested by Evans[68] as follows:

" The hands must be thoroughly cleaned always before eating or smoking. To remove radium paint from the hands Dr. George E. Morris has tested a number of solvents. He has found most effective and least toxic a mixture of 1 part xylene, 1 part trichlorethylene and 2 parts ethyl alcohol. This mixture should be rubbed onto the dry skin and removed, before it evaporates, with soap and water. The skin then is thoroughly dried and examined in a darkened room under ultra violet light, which will reveal any residual luminescent material. If the first cleaning is not complete, as is often the case, the entire solvent and washing process is repeated until the ultra violet lamp reveals no residual radium paint. In the dark room many of the new ultra violet lamp bulbs will be found satisfactory. For example, the GE 4 watt RP-12, 360 BL lamp can be obtained in a convenient fixture (Grimes Mfg. Co., Urbana, Ohio) including a filter for removing visible light. If a more powerful but less portable source is desired, the GE type BH4 (sunlamp with filter to remove visible light) may be installed. These new lamps are more suitable than the argon glow lamp because the latter gives more visible light and less ultra violet radiation.

" One wash basin, with solvent, soap, hot and cold water and paper towels should be provided for every five workers. A waste receptacle provided with a swinging lid operated by a foot pedal should be provided for used towels. In very large plants one wash basin per ten to fifteen active workers may suffice, especially if rest periods and lunch hours are staggered. The washing and dark room areas are most useful if adjacent to one another. Local ventilation should be provided in both areas to remove solvent fumes.

" A separate sink should be provided for the disposal of contaminated solvents, which have been used to wash radium compound from imperfect or discarded work."

The other group involved in the radium room is that composed of inspectors, foreman and those who clean the room. These are exposed likewise to the dust and need just as careful supervision in hygiene.

In order to make certain that the worker is not absorbing too much radium,

two routine procedures are in order. One of these is to do a complete blood count once a month. The other is to have the worker undergo breath radon measurements. The reader is referred again to the article by Evans[68] for details of this measurement.

In the further prevention of radium absorption it is felt that an adequate intake of calcium is of value. This is based upon belief that radium metabolism closely parallels that of calcium. On the other hand, if a worker reveals the presence within the body of excessive radium, then excretion of radium is aided by a low calcium intake.

In chronic radium poisoning a régime directed towards aiding in the excretion of radium should be followed. It is suggested that a low calcium diet, parathyroid extract and large doses of ammonium chloride be instituted. That such treatment will have much effect is to be questioned. Treatment of any existing anemia is also advisable.

Lead

Absorption. — Lead enters the body either through the lungs, by ingestion or possibly through the broken skin, although this last mentioned route is insignificant and industrially not important. Nor does lead poisoning occur frequently from ingested lead, whether the environment be industrial or not. Any acute illness attributed to the ingestion of lead deserves a thorough investigation to make certain that some other ingredient was not the actual cause of the illness. In 1930 Kehoe[159a] placed two students upon a prolonged regimen of increasing oral doses of soluble lead, one receiving 2 mgm. for a period of 6 months, the other 1 mgm. for a period of 30 months. His study included laboratory data of the microscopic blood smears, excretory response and changes in the level of lead concentrations in the blood and urine. Neither subject studied revealed any symptoms of plumbism. Occasionally a clinician reports plumbism from ingested lead, in which the study has been so scientifically thorough as to accept such instances as authentic, as in the report of Magnuson and Raulston[195a]. The men they observed had been in the habit of holding in their mouths roofing nails, which were fourteen gauge "hot dip" galvanized nails containing lead from 0.9 to 4.7 per cent. in the zinc coating.

Except for the exceedingly rare case, then, it is the inhalation of lead fumes or dust, which causes lead intoxication, and almost invariably it is from the fumes, since the fumes are less conspicuous, whereas a dusty atmosphere immediately bespeaks bad housekeeping and is more apt to lead to steps for its eradication. However, the worst case of lead intoxication ever seen by one of us (Johnstone) was that of lead encephalitis due to prolonged exposure to heavy concentrations of lead dust.

Storage. — The eventual fate of lead once it has entered through the lungs to reach the circulating blood is a controversial question, too involved for detailed discussion here. The opinions of various investigators have been reviewed elsewhere[156]. Following the original work of Aub and his co-workers[4b, 5, 6], it has been generally believed that lead was transported as finely divided colloidal lead phosphate to be deposited as a tertiary lead phosphate in the bones. Subsequently Aub, Robb and Rossmeisl[6a] stated that most of the lead was stored in the trabeculae, not the cortex of the bone. They contended that, since the trabeculae act as a storehouse for calcium, the lead stored here was mobilized or freed according to calcium metabolism. This opinion introduced the popular calcium therapy about which more will be mentioned later. To Kehoe and Thamann[160a] the idea that lead is fixed in stable form in the skeleton, either normally or through any kind of therapy, is untenable. For practical purposes suffice it to state that it is the accumulation of lead within the blood and tissues of the body which causes symptoms of lead intoxication; that following the withdrawal of the patient from his exposure, lead is excreted in sufficient amounts as to permit the subsidence of symptoms. If certain amounts of lead are actually stored in the bones or elsewhere, it has little subsequent effect upon the individual.

Because the treatment of lead intoxication is intimately related to the question of storage and elimination, further consideration of these factors will be entertained in the discussion of the treatment of plumbism.

Prophylaxis. — As with all cases of occupational intoxication that from lead is unwarranted. Infrequent in the larger, well supervised plants, these cases occur usually in small plants where the principles of industrial hygiene are ignored. In addition to the following measures suggested for routine plant adherence it would be well for exposed workers to drink adequate amounts of milk daily and to maintain good intestinal elimination. By all means constipation is to be avoided in lead workers.

The best method to avoid lead poisoning is, of course, to take measures to prevent it. To this end Gant[85a] suggests the following rules and mechanical features:

1. Hoods with adequate exhaust ventilation to be at any point where dust or fumes arise.
2. All mixing and shaking to be done in enclosed machines.
3. All powdered compounds to be transferred by means of adequate vacuum lines.
4. Work tables to be provided with grated tops, ventilated from below, and equipped with small narrow troughs filled with water and attached to each side to prevent dust falling to the floor.
5. All inlets to exhaust ventilating ducts to be below the level of the nose as far as possible to prevent fine dust particles from being inhaled.

6. A chemical analysis of samples of air from various parts of the plant to be made at different intervals during working hours. Any spot showing more than 1.5 mgm. of lead per 10 cu. m. is a potential health hazard.
7. Employees in hazardous spots as found under "6" to wear respirators. Where movements are confined to a small area, forced-draft respirators, fresh air from the outside, to be used. If exposure is to fumes, masks to be provided with canisters charged with activated carbon. Respirators are only from 70 to 90 per cent. efficient and must be inspected and changed frequently.
8. No dust allowed to accumulate on the floor.
9. Floors to be wet at frequent intervals and powdered compounds used, if possible.
10. All cleaning to be done with large vacuum lines. No sweeping.
11. To prevent the collection of dust on rafters, sills, etc. ventilating ducts to be installed, equipped with dust-filters near the ceiling or in mid-air.
12. To avoid the contamination of outside air and surrounding territory and as an economy measure electrostatic precipitators to be installed in the stacks and flues.
13. The personal hygiene of the employees to be closely guarded. Locker rooms with showers, a lunch room isolated from the plant and a change of overalls twice a day to be provided. Hands and face to be washed before eating. No eating, chewing or smoking during working hours.

Treatment. — Before having the reader become involved in the arguments supported by the various investigators in this field regarding the basis for treatment of lead intoxication, the author of this portion of the text wishes to describe a very simple and workable régime used at the Golden State Hospital in Los Angeles. Since this is an industrial clinic, to which come all types of occupational diseases, the incidence of true plumbism is considerable. Since 1936, when the author became affiliated with this clinic, until 1941 there were admitted annually for treatment an average of 54 patients. This took a sharp upturn following the war and during the first ten months of 1944 113 cases were seen. From 1936 until 1939 the treatment followed in general the teachings of Aub. Since then that régime has been abandoned in favor of the following method:

1. All patients with proven plumbism are withdrawn immediately from their occupational exposure. Even if the clinical and laboratory findings indicate a questionable or borderline case, the worker is transferred to a type of work involving no exposure to lead.
2. In those cases with mild intestinal colic calcium is given by mouth, good intestinal elimination encouraged and the patient advised to continue to work.
3. In cases of severe intestinal colic the patient is hospitalized and intravenous

calcium therapy instituted. This is continued until the more violent colic has subsided at which time calcium by mouth is given. All calcium therapy is stopped upon the cessation of intestinal discomfort.

4. To the general hospital diet 20 minims of viosterol daily is added.

5. For the anemia, which invariably is present in the severe cases, ferrous sulphate is prescribed.

Under this régime we have not found it necessary to resort to morphine, atropine sulphate, nitroglycerin or amyl nitrite, all of which are referred to in the subsequent review of the methods of treatment.

The success of the treatment just outlined indicates that the symptoms from lead intoxication subside because (1) the patient has been withdrawn from his exposure, thus preventing any further accumulation of the noxious substance, and (2) he rapidly eliminates the lead from his body. One case in particular is of interest in this regard. A patient with a severe degree of lead encephalitis was relieved of his nervous and cerebral symptoms by two spinal fluid taps. He received no calcium and recovered completely. Since his lead intoxication he has had pneumonia on one occasion and on another a septicemia without any evidence of exacerbation of his so-called "stored lead".

The almost instantaneous relief of lead colic following the use of calcium leaves little doubt that this drug has a physiological effect upon the smooth muscle of the intestinal tract, but the action is too sudden and dramatic to cause anyone to believe that the quick relief is due to the immediate storage of lead within the bones of the body. It is our considered opinion that once the calcium has caused the colic to cease, its utility is ended.

As promised in the opening paragraph under treatment the following opinions held regarding the treatment of lead intoxication now will be outlined.

Deleading by High Calcium Diet: Following the work of Aub, Fairhall, Minot and Reznikoff[5], which indicated that lead could be either stored or excreted by distorting the calcium metabolism, therapy was directed along these lines. The conclusions drawn from their work were that a negative calcium balance increases the rate of lead excretion, while a positive calcium balance favors the storage of lead. To this end then the treatment for the acute episode in the past consisted of the following:

1. A high calcium diet, which includes much milk, green vegetables and potatoes.
2. The administration of calcium products and vitamin D orally, e.g., calcium lactate, 1 drachm (4 gm.), once every two hours, or calcium gluconate, $7\frac{1}{2}$ grains (0.5 gm.), in milk at three-hour intervals, so that the patient obtains five or six doses daily.
3. Calcium gluconate, 10 c.c. of 10 per cent. solution, intravenously daily for five days.

4. Magnesium sulphate, ½ ounce every morning, to sweep out the relaxed bowel.
5. As substitutes for the intravenous calcium gluconate in the relieving of abdominal pain, hypodermic injections of morphine sulphate, ¼ grain (15 mgm.), and atropine sulphate, $\frac{1}{100}$ grain (0.6 mgm.); nitroglycerin, from one to two $\frac{1}{100}$ grain (0.6 mgm.) tablets dissolved under the tongue or the inhalation of the contents of a 5-minim (0.32 c.c.) amyl nitrite pearl.

Disadvantages of Method. — Recently much doubt has been thrown on this method of treatment by the work of Lederer and Bing[180e]. Their work indicated that the deposition of lead in the bones of growing animals is retarded by increasing the calcium content of the diet, and that the phosphorus content of the diet had no significant effect on the amount of lead deposited in the bones. This would indicate then that a high calcium diet would be the optimum diet for deleading rather than for the deposition of lead in the bones. The use of the high calcium diet according to this view might actually be dangerous by mobilizing lead for possible storage in the central nervous system in the acutely ill patient. Taeger[306c] arrives at such a conclusion and advises against large doses as well as against the intravenous administration of calcium. Shelling and Hopper[286b] believed the use of calcium did not induce superior calcification but rather had the opposite effect, especially when the phosphorus intake was inadequate. Kehoe and Thamann[160a] were of the opinion that the use of agents to promote the quick release of lead from the tissues was hazardous. Shelling[286a] demonstrated experimentally that the addition of calcium carbonate to an optimal stock diet containing lead carbonate fed to rats resulted in an increased toxicity. These rats evidenced toxicity and died sooner than the rats fed on the same stock diet to which sodium phosphate had been added. Gray and Greenfield[96c] reported a small series of cases, where prolonged administration of high calcium diet therapy was responsible for permanent, irreparable damage to the nervous system. They concluded that a high calcium regimen was the best means of deleading. In view of this evidence the advisability of the use of high calcium diet alone is open to question. The frequently dramatic relief of abdominal pain obtained from the intravenous administration of calcium may represent, then, only a general depressant action of calcium on smooth muscle rather than a specific reaction as regards the lead in the bloodstream.

Optimal Calcium Diet with High Phosphorus and High Vitamin. — Gray and Greenfield[96c] found the use of an optimal calcium diet with a high phosphorus and high vitamin diet, particularly D, the best treatment in these cases. With this regimen an essential element was the administration of sodium phosphate, two drachms (8 gm.), three times daily. Shelling[286a] indicated that in order to deposit lead in the skeleton as an insoluble lead phosphate a certain amount of phosphate was required, and thus when phosphate was inadequate, free lead

might remain in circulation. He stated that the addition of sodium phosphate "provides sufficient phosphate for the deposition of both calcium and lead phosphosin the skeleton, for the excretion of lead as the relatively non-toxic lead phatephate and also for the formation of colloidal lead phosphate in the blood." As indicated, the work of Lederer and Bing[180e] directly opposes this statement and seems to indicate that the addition of phosphate had no significant effect. The work of Lederer and Bing[180e] further indicated that the beneficial effect of calcium in the diet in retarding the retention of lead by the body was due to reactions which occurred in the intestinal tract, and that calcium carbonate orally was the most valuable preparation.

Deleading by Low Calcium Diet with High Phosphorus. — In the past a regimen of a low calcium high phosphorus diet, phosphoric acid and magnesium sulphate had been used successfully by Gray[96b] in deleading treatment.

He also elaborated a similar diet with a calcium to phosphorus ratio of 1:4. To these were added 20 minims of viosterol (250 D) daily, since vitamin D was deficient in the diet. Previously he had used a low calcium diet consisting of meat, liver, potato, rice, tomatoes (cooked without milk), canned corn, bananas, apples (peeled), tea, coffee (without milk), butterfat, bread (prepared without milk, such as salt-free nephritic bread or sodium bicarbonate biscuits or crackers), sugar, salt and pepper. Phosphoric acid in amounts of from 10 c.c. every two hours for six doses daily to 10 c.c. once every hour for ten doses daily was used. In addition, magnesium sulphate, ½ ounce (15 gm.), was given each morning. With this regimen, increase in urinary lead was seen at first, and this was followed by a decrease as the patient was, presumably, deleaded.

Other Methods. — Other methods suggested for deleading have included the low calcium diet cited above, ammonium chloride, 15 grains (1 gm.), every hour for ten doses daily and magnesium sulphate, ½ ounce (15 gm.), every morning. Belknap[12d, 12e] used 15 drops of potassium iodide twice daily or 7 drops of sodium iodide twice daily both in saturated solution. Sodium bicarbonate, from 5 to 8 drachms (20 to 30 gm.), daily, divided into five or six portions, has been used also as has parathyroid extract.

Advisability of Deleading. — As indicated above there is disagreement concerning the possibility of deposition of lead in bones by changes in diet or by medication. In addition, the advisability as well as the possibility and the methods of deleading is distinctly open to question. Most authorities feel that it should not be attempted before from three to four weeks have elapsed after the acute episode. Most feel that the deleading should be carried out only in the hospital and with adequate laboratory checks, although Belknap[12d], cited above, deleads patients in mild cases while they are ambulatory but under close supervision. He requires a blood level of 80 per cent. hemoglobin, 4,000,000 or more red blood cells, stippled cells not more than from 1,000 to 5,000 per million red blood cells for two

to three weeks and a twenty-four-hour urine lead 0.15 mgm. or lower before undertaking the deleading. He also deleads no oftener than once in four weeks and preferably not oftener than once in six or eight weeks.

Benefits versus Drawbacks of Deleading. — Those who oppose deleading feel that the danger of producing lead encephalopathy is too great, and that at any rate the patient cannot be "deleaded" successfully. Those who favor it urge that the stored lead represents a constant potential hazard, since acute episodes such as infections with acidosis or other periods of metabolic stress may cause deleading at an undesirable time. Aub[4a] feels that thorough deleading approximately halves the period of disability for lead palsies.

Ascorbic Acid Therapy. — A few investigators, notably Holmes, Campbell and Amberg[140a], have contended that daily administration of ascorbic acid is of benefit in treating lead intoxication. Most investigators, however, have found this adjunct to have negative results. The Cincinnati group at the Kettering Institute[67b] during their study of nutrition of industrial workmen found ascorbic acid deficient in a majority, and in lead workers it was below the average, but they found also that the administration of ascorbic acid had negative results in plumbism.

Treatment in Lead Palsy. — In this condition stretching of fibers of paretic muscles should be prevented. In those cases presenting a wrist-drop a cocked-up splint to include the fingers and worn night and day is used until function returns. Hot-water baths (110° F.), electric stimulation by interrupted galvanic current and gentle massage, preferably by whirlpool, once every day or two are used. Strenuous massage and violent exercise are avoided. Reëducation exercises are of value.

Treatment in Lead Encephalopathy. — Encephalopathy is rare and has been seen only once in our clinic in the past five years. When it does occur, lumbar puncture and sedation may be required. Magnesium sulphate, 2 c.c. of a 25 per cent. solution, given intramuscularly for every four to six hours, and barbiturates are used. For convulsions barbiturates, e.g., sodium amytal, from $\frac{3}{4}$ to $7\frac{1}{2}$ grains (0.23 to 0.5 gm.), are given intravenously, and avertin is used rectally. Suboccipital or subtemporal decompression in lead encephalopathy has been used successfully.

In conclusion, despite the expression of opinions just presented, it is the author's opinion that the treatment of lead intoxication requires therapy for the acute condition only. Attempts to store lead or to delead a patient are unnecessary and may be, in the case of deleading, dangerous.

Carbon Monoxide

Treatment. — *Acute Anoxemia.* — When this occurs, the victim should be removed immediately from his exposure and artificial respiration begun by the

Schaefer prone pressure method of resuscitation. It is extremely important, however, that inhalations of 5, 7 or 10 per cent. carbon dioxide in oxygen be started early and continued for 15 to 30 minutes or even longer to obtain deep breathing. The carbon dioxide not only increases the volume of breathing but also aids in the disassociation of carbon monoxide from the hemoglobin. The inhalations should be increased to the point where full, deep inspirations are obtained from the patient. All emergency squads, which are called frequently to attend such cases, should be equipped with this carbon dioxide and oxygen mixture with inhalation apparatus for its administration. If such apparatus is immediately available, the patient should be kept warm with blankets and hot-water bottles and treated at the spot rather than be moved to the hospital with attendant delay in the administration of the inhalations. It should be remembered that probably half of the carbon monoxide is eliminated from the body during the first hour after removal from the exposure, and consequently long-continued administration of the carbon dioxide and oxygen may not be required. If such inhalations are not available, the patient should be transported to a hospital, where they can be obtained, and en route it is necessary to continue the artificial respiration.

Koch[164a] recommended blood transfusions preceded by venesection in severely acute cases. He pointed out that the chief effect of carbon monoxide poisoning was the anoxemia, and therefore, the hemoglobin introduced by means of the blood transfusion will act at once as an oxygen vehicle.

Methylene blue, once thought to be an antidote, is not of value and is now thought to be harmful. With the possible exception of caffeine, it is felt that the use of drugs is ineffectual, if not actually harmful. Strychnine, camphorated oil, digitalis, pituitary extract, adrenalin, alpha-lobeline and morphine fall into this category.

The use of 12 ounces (350 c.c.) of physiological solution of sodium chloride given by rectum every four hours during the first few days has been suggested, as has the rectal administration of a 4 per cent. sodium bicarbonate solution.

Hydrogen Sulphide

Prevention. — Whenever it is known that this substance is apt to be present in any industrial process, workmen should be forced to wear specially designed protective masks to prevent inhalation of the gas. The eyes likewise should be protected against irritation. All processes should be conducted under adequate exhaust conditions.

Treatment. — *Combating Respiratory Failure.* — In severe poisoning chief attention is directed to the respiratory failure, which appears to be due to depression of the respiratory center. The patient should be moved at once from the point of contact with the gas and fresh air provided. Artificial respiration should

be started at once, and as soon as available inhalations of mixtures of from 5 to 7 per cent. carbon dioxide with oxygen are to be commenced. The use of respiratory stimulants, such as caffeine sodium benzoate, 7½ grains (0.5 gm.), coramine, 0.5 c.c., intramuscularly or preferably intravenously, and metrazol, 1½ grains (0.1 gm.), may be of value, but it is questionable if these are of value in severe cases unless adequate respiration has been established by artificial respiration or by the oxygen-carbon dioxide inhalations. Bronchitis and bronchopneumonia may appear as complications and require the ordinary treatments for these conditions.

Care of Eyes. — The eyes may be severely irritated, and the condition may even go on to the development of corneal ulcers. As with other irritants to the eyes, e.g., ammonia, they should be thoroughly washed at once with water. Following this, the use of a saturated boric acid solution and of olive oil is advised. Local anesthetic solutions such as 2 per cent. butyn or 0.5 per cent. pontocaine hydrochloride may be used in relief of pain. Continuous warm boric compresses may be of value in preventing further complications. When available, the advice of an ophthalmologist should be sought.

The Petroleum Distillates

Treatment. — *Acute.* — Invariably these cases are acute, and the treatment must be designed to prevent respiratory and circulatory collapse. When the exposure has been intense, pulmonary edema and alveolar damage may be expected early. For such conditions positive pressure therapy is the method of choice. The clearing of the edema and the rapid recovery in these and in edema from other pulmonary irritants is so startling as to consider this type of treatment almost specific.

If positive pressure cannot be induced, then oxygen by catheter, mask or tent should be resorted to early. If the mask is used without positive pressure, the development of negative pressure resulting from the collapsing rubber bag must be avoided.

Positive pressure respiration is urged, and the positive pressure should be from 2 to 6 cm. of water. A mask of the meter type (see section on Inhalation Therapy) can be used with resistance provided at the end of expiration. By this method positive pressure may be obtained by exhaling through a constricted orifice. Barach advises that the patient be subjected to a pressure of 4 cm. of water until signs of edema clear, after which the pressure may be lowered gradually.

If the patient's clothing is saturated with these noxious substances, these should be removed and the body cleansed and dried. The patient should be wrapped in blankets and kept warm. At this time circulatory failure, if present, should be treated by any of the following drugs, coramine, 1.5 c.c., caffeine sodium benzoate, 7½ grains (0.5 gm.), or metrazol 1½ to 4½ grains (0.1 to 0.3 gm.)

intramuscularly. The coramine and metrazol may be used intravenously and will also act as respiratory stimulants. Artificial respiration usually is felt to be contraindicated because of the existing lung damage, and adrenalin administration has been found to give poor results.

Prevention of Pulmonary Complications. — The lungs especially need to be watched for complications, such as bronchopneumonia. After the first portion of the acute stage, where respiratory stimulation chiefly is needed, oxygen therapy may be substituted for the carbon dioxide and oxygen inhalations. For cough codeine phosphate or sulphate, ½ to 1 grain (30 to 60 mgm.), perhaps in a cough-syrup vehicle, is useful.

Nervousness and Restlessness. — These conditions may require sedation by any of the following drugs; chloral hydrate, 10 to 30 grains (0.6 to 2.0 gm.), phenobarbital, 1½ grains (0.1 gm.), sodium bromide, 10 to 30 grains (0.6 to 2.0 gm.), or paraldehyde, 2 to 4 drachms (8 to 16 c.c.). The paraldehyde may be mixed with elixir lactate pepsin, poured over crushed ice and administered by mouth, or it may be given rectally in olive oil with 1.5 c.c. benzyl alcohol. Magnesium sulphate, 1 ounce (30 gm.), should be given.

Venesection followed by blood transfusions to rid the body of methemoglobin has been advocated. When ingestion of the substance has occurred, lavage with magnesium sulphate solution is of value.

Conjunctivitis. — Due to irritation from petroleum distillate fumes, conjunctivitis may be treated by dropping 1:1,000 adrenalin solution into the eyes four times a day, followed by the use of cold applications for from 10 to 15 minutes. Bland boric acid ophthalmic ointment should be used also.

Chronic Cases. — Patients in chronic cases chiefly need removal from their exposure. The diet should be high in calories with added vitamin preparations. For the secondary anemia ferrous sulphate, 5 grains (0.3 gm.), two tablets three times a day, may be used. The ferrous sulphate preparations seem effective in relatively small doses, and they also seem to cause less gastrointestinal discomfort than other iron compounds.

Oxygen Therapy in the Acute Occupational Intoxications

Although the physical and chemical characteristics of the various gases have been studied for many decades, their therapeutic application did not occur until after the investigations of Van Slyke, Haldane, Boothby, Barcroft, Henderson, Haggard, Barach and a few others. Barach[9c] in particular has demonstrated the value of oxygen, carbon dioxide and sometimes, helium in the treatment of cardiac failure, coronary artery disease, pneumonia, pulmonary edema, emphysema, atelectasis and asthma. While general medicine has accepted this type of therapy, industrial medicine has not utilized it to the degree warranted.

Following an undue exposure to certain industrial chemicals, the pathology found in the lungs is not dissimilar from that found in various respiratory and cardiac diseases of non-occupational origin. In these latter conditions the oxygen want is due to the inability of the lungs to diffuse oxygen or the heart to circulate oxygen in the blood. This is true likewise of the industrial agents, which may act as an asphyxiant, as an irritant to the lungs or as an anesthetic to the respiratory center in the brain. Regardless of the manner of action, the result is anoxemia. It is to combat this anoxemia that oxygen therapy is of value. When resorted to, oxygen enriched atmospheres containing 40 to 60 per cent. oxygen will raise the oxygen saturation of arterial blood to near normal levels.

Carbon dioxide likewise is a common therapeutic agent. Ever since Haldane, Priestley and Douglas contended that the volume of breathing is controlled by the percentages of carbon dioxide in the air within the lungs, percentages of this gas have been employed to stimulate respirations. Yet, if the writer interprets the observations of Barach correctly, the general use of carbon dioxide is not only of questionable value in many instances but likely to be harmful. Barach and his co-workers would discourage its use in the treatment of most cardiac and respiratory diseases except for post-operative atelectasis, hiccoughs and accidental asphyxia.

In Barach's recent excellent book[9c] he gives but scant space to the treatment of the occupational disturbances of the lungs. Yet it has been the writer's experience that oxygen therapy is of great value in immediate treatment of the acute effects from undue exposure to sulphur dioxide, phenol, ammonia, nitric acid and nitrous fumes and cadmium. All of these are capable of producing a marked pulmonary edema. Carlisle[33] likewise found that oxygen gave striking results in the treatment of pulmonary edema due to chlorine and nitric acid.

Broadly, the chemical agents used in industry which may affect the respiratory system are:

1. The irritants: The most common of these are chlorine, bromine, ammonia, nitrous fumes, chloropicrin, phosgene, diphosgene, sulphur dioxide and cadmium. Exposure to high concentrations of these may result in pulmonary edema, bronchiospasm, bronchiopneumonia and concentration of blood in the pulmonary vessels.

2. The asphyxiants: These are primarily carbon monoxide, cyanide and hydrogen sulphide. With carbon monoxide asphyxia is produced by the displacement of oxygen within the blood by the noxious gas. Therefore, the more quickly the disassociation is attacked, and the normal relationship of oxygen to hemoglobin takes place, the less permanent damage will occur. It is in this type of case that carbon dioxide should be combined with oxygen in amounts of 5, 7 or 10 per cent. The carbon dioxide stimulates the respiratory center to produce full, deep respirations and thus relieves the anoxemia.

Recently the investigations of End and Long[66a] indicate that pure oxygen under pressure is of greater value than is the carbon dioxide oxygen mixture. By animal experimentation they show that carbon monoxide causes tissue damage by producing an anoxia, and that current methods of treatment are unable to correct this anoxia. Inhalation of oxygen under three atmospheres of pressure is capable of preventing such anoxia by causing solution of enough oxygen in the blood to provide for the needs of the tissues. Inhalation of oxygen under three atmospheres of pressure for several hours is safe.

The first action of hydrogen sulphide is upon the respiratory center. In a person overcome by these fumes respirations will cease before the heart action stops. It is, therefore, imperative to stimulate the respiratory center by carbon dioxide-oxygen inhalations and/or by artificial respiration.

Oxygen is of little or no value in cyanide poisoning, since cyanide, instead of combining with the hemoglobin in the blood stream, retards oxidation in the tissue cells.

3. The anesthetics: A large group of solvents used in industry gives off vapors which affect the central nervous system by producing an anesthesia. Of these the most common are carbon tetrachloride, trichlorethylene and the petroleum distillates. In the average case these do not cause any pathological change within the lungs proper, although the petroleum distillates have been known to cause pulmonary edema and one of us (Johnstone[156]) had a case in which pleural effusion resulted after a massive dosage of gasoline. Just as in operative anesthesia an overdosage of these gases produces unconsciousness which demands immediate oxygen therapy.

It should be pointed out to the reader that in cases of pulmonary edema from any cause, occupational or non-occupational, the mere utilization of oxygen is not sufficient. The best results are obtained only if oxygen is administered under positive pressure. While all physicians are acquainted with the nasal catheter, various masks, oxygen tents and oxygen rooms, the apparatus for positive pressure needs explanation:

> "The oxygen-injector mask metered for positive pressure is designed solely for the treatment of pulmonary edema due to cardiorespiratory illness or gas poisoning. It should be employed cautiously in patients with shock (Barach[9c]).
>
> "The injector mask has been equipped with a metal disk that surrounds the expiratory flutter valve and contains on its surface five orifices of varying diameters. Expiration proceeds naturally without pressure when the largest orifice is employed. When the disk is turned to progressively smaller orifices, the patient exhales under a positive pressure which is 1, 2, 3 or 4 cm. of water, depending upon the size of the orifice. These pressures have been recorded during quiet breathing and would be higher in dyspneic patients. It will be

found that expiration at a pressure of 4 cm. of water is uncomfortable and can be used for short periods only. However, a swifter clearance of pulmonary edema, especially in chlorine and nitric acid gas poisoning, may be obtained, when the higher pressures are used for short periods. In pulmonary edema taking place during the course of clinical illness 3 cm. of water may be adequate to result in a disappearance of the signs of moisture in the lungs, and a smaller pressure of 1 to 2 cm. of water then may be used for periods of one to three hours as may be required. Return of signs of moisture in the lungs indicates reapplication of positive-pressure breathing.

"In order to employ 100 per cent. oxygen a high liter flow such as 12 to 15 liters per minute is necessary to prevent collapse of the collecting bag. Under these circumstances it is desirable for the injector to be one-third full of water so that the oxygen may pick up some moisture as it passes through. Test of the relative humidity of 100 per cent. oxygen passing over the water surface in the injector has shown a relative humidity of 20 per cent. of the air entering the mask. However, it has also been demonstrated that additional moisture is contributed to the inspired air, because the inner surface of the mask is itself wet with moisture, which has condensed on it from the expired air, and the actual relative humidity of air entering the mask under these circumstances is 40 per cent. If a higher relative humidity is desired during the inhalation of 100 per cent. oxygen, either with or without positive pressure, the injector may be removed and a water bottle attached to the regulator. The oxygen then passes through 2 or 3 inches of water and possesses a higher relative humidity.

"The patient may be treated with 50 or 60 per cent. oxygen and the positive pressure desired by setting the injector and pressure dials at the appropriate orifices. This results in considerable saving of oxygen and is a therapeutically effective, efficient and practical procedure. Although a swifter clearance of edema of the lungs may be obtained by expiration at high pressures, it is frequently desirable to employ lower pressures, such as 2 to 3 cm. of water, even though a longer time is necessary for complete clearance of the signs of edema. This is in part because of lessened discomfort to the patient but also because low pressures do not significantly retard the entrance of blood into the right heart. In patients with cardiac illness such as congestive heart failure, the retardation of blood is comparable to tourniquetting the extremity and facilitates the recovery of the heart muscle by making it possible for the heart to work on a smaller volume of blood.

"However, in patients with peripheral circulatory failure, pressures of 1 cm. of water may be employed in the attempt to eliminate pulmonary edema without causing any significant decrease in return of blood from the right heart. The systolic blood pressure should be carefully recorded at 10–minute

intervals in all patients with shock. When pulmonary edema has cleared, the patient may breathe 60 to 100 per cent. oxygen without pressure. If no recurrence of edema takes place, and the patient is clinically better, the injector may be turned to 50 per cent. oxygen and then to 40 per cent., and the mask may be finally removed, when the clinical condition of the patient indicates that he is out of danger. If pulmonary edema recurs after termination of positive pressure, the pressure should be applied again at 3 cm. of water and then gradually lowered at longer intervals."

It is hoped that this rather concise discussion of oxygen therapy will focus the attention of the industrial physician upon an exceedingly valuable and often life-saving aid in the treatment of respiratory affections due to the inhalation of certain noxious vapors or fumes. Too frequently workers, who are overcome by such agents, are given ineffectual smelling salts, hypodermics of indiscriminate medication or are subjected to an interim of neglect while awaiting transportation to a hospital. Nor is hospitalization always assurance that oxygen therapy will be instituted upon the patient's arrival, since the pathology of the occupational respiratory affections is not too well known by the attendant staff of the average non-industrial hospital. The industrial physician would do well to specify the type of treatment he desires when referring cases to such institutions.

Part III

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